FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

WEDNESDAY, NOVEMBER 2, 2011

8:00 a.m. to 3:30 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. BALIS: Good morning. I'm Frank Balis. I'm a pediatric oncologist from the Children's Hospital of Philadelphia, and I'll be chairing the session this morning.

We have a new group of people in since yesterday, so why don't we go around again and introduce ourselves. Maybe, Dr. Reaman, you can start from your side.

DR. REAMAN: Sure. I'm Greg Reaman, a pediatric oncologist and associate director of the Office of Hematology Oncology Products.

DR. FARRELL: I'm Ann Farrell. I'm the acting division director of the Division of Hematology Products.

DR. ROBIE SUH: Kathy Robie Suh. I'm a medical team leader in the Division of Hematology Products.

DR. DURMOWICZ: Good morning. I'm Beth

Durmowicz. I'm a medical officer on the Pediatric and Maternal Health staff here at FDA.

MS. MCMILLAN: Good morning. I'm Gigi McMillan, subject representative.

DR. NEVILLE: I'm Kathleen Neville. I'm hemoc and clinical pharmacology from Children's Mercy Hospital.

DR. SHEARER: I'm Patty Shearer, pediatric oncologist from the University of Maryland Greenebaum Cancer Center in Baltimore.

DR. FREEDMAN: Ralph Freedman, gynecologic oncologist, M.D. Anderson Cancer Center, and standing member of ODAC.

DR. BRIGGS: Caleb Briggs, designated federal officer, ODAC.

DR. SEKERES: Mikkael Sekeres, medical oncologist, Cleveland Clinic.

DR. SHURIN: Susan Shurin, acting director of the National Heart, Lung, and Blood Institute at NIH.

DR. LUBAN: Naomi Luban, pediatric hematologist and director of laboratories, Children's National, Washington, D.C.

DR. ARTMAN: I'm Mike Artman. I'm a pediatric cardiologist and pediatrician and chief at Children's Mercy Hospital in Kansas City.

DR. KASKEL: Rick Kaskel. I'm a pediatric nephrologist, director of the division at Albert Einstein Montefiore in New York.

DR. CURT: Gregory Curt, medical oncologist and industry representative to ODAC.

DR. BALIS: It sounds like there's something wrong with those microphones or you need to clear your throats.

[Laughter.]

DR. BALIS: I'm not sure which.

All right. Well, let me read the disclaimer statement this morning or the instructions, I guess I should say, and then we'll move on to some of these interesting presentations.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that

individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

I would like to remind everyone present to please silence your cell phones and other electronic devices if you haven't already done so. And the committee is reminded to please refrain from discussing our meeting topic during breaks or lunch. Thank you.

Caleb?

Conflict of Interest Statement

DR. BRIGGS: The Food and Drug Administration, FDA, is convening today's meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all members and temporary members of the subcommittee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this subcommittee's compliance with federal ethics and conflict of interest laws, covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug & Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary members of this committee are in compliance with federal ethics and conflict of interest laws. Under

18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflicts of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the subcommittee essential expertise.

Related to the discussions at today's meeting, members and temporary members of this subcommittee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary

employment.

Today's agenda involves discussions related to regulatory, academic, and industry perspectives regarding the development of anticoagulant products in children. Issues for discussion will include identification of strategies to encourage and facilitate studies of anticoagulants in children that will result in informative pediatric labeling, appropriate endpoints for studies of anticoagulants in pediatric patients, and the role of pharmacokinetic/pharmacodynamic studies to support a pediatric indication for anticoagulants.

This is a particular matters meeting during which general issues will be discussed. The subcommittee will not be voting. Based on the agenda and all financial interests reported by the subcommittee members and temporary members, no conflict of interest waivers have been issued in connection with this session.

To ensure transparency, we encourage all standing subcommittee members and temporary members to disclose any public statements that they may have

concerning the product at issue.

With respect to FDA's invited acting industry representative, we would like to disclose that Dr. Gregory Curt is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Curt's role at this meeting is to represent industry in general and not any particular company. Dr. Curt is employed by AstraZeneca.

With regards to FDA's invited guest speaker, the agency has determined that the information to be provided by this speaker is essential. The following relevant interests are being made public to allow the audience to evaluate objectively any presentation and/or comments made by the speaker. Dr. Ron Portman is employed by Bristol-Myers Squibb and holds stocks in firms that could be affected by today's discussions.

We would like to remind members and temporary members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed

financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firms at issue.

Thank you.

DR. BALIS: So we'll now proceed with FDA's presentation.

Dr. Donoghue, would you introduce yourself before you start?

FDA Presentation - Martha Donoghue

DR. DONOGHUE: Good morning, and thank you for participating in today's pediatric subcommittee meeting. My name is Martha Donoghue, and I'm a medical officer in the Office of Hematology and Oncology Products at FDA.

FDA is holding this meeting to address an important public health issue, the need for additional research-based guidance to enable the consistent, safe, and effective use of anticoagulant drug products in children.

The objectives of today's meeting are to obtain input from academic and industry experts regarding current approaches to the treatment of pediatric thrombosis and identify and prioritize which types of anticoagulant products, indications, and age groups should be further studied. In addition, we seek input from the panel regarding the study design and endpoints that should be used in future studies, as well as strategies to facilitate the conduct of studies that would result in informative pediatric anticoagulant labeling.

To provide a context for today's discussion, I will first give a brief introductory presentation on pediatric thrombosis. Following this presentation, we will hear perspectives on the development of anticoagulants for use in pediatric patients presented by FDA, two pediatricians with backgrounds in academic medicine who treat pediatric thrombosis, and an industry representative who has experience in pediatric anticoagulant research.

Following these presentations, we will hear about existing resources at NHLBI, which may be

helpful in conducting future studies. After these talks, FDA will pose key questions and topics for discussion by the subcommittee.

I am now going to provide some background information regarding the epidemiology of thrombosis in children, followed by a snapshot of current treatment approaches and challenges, as well as an overview of newer classes of anticoagulants that are currently approved for adults that may provide benefit to pediatric patients.

Data compiled from a handful of national and international pediatric thrombosis registries indicate that thrombosis is relatively rare in children and occurs at a rate of approximately 0.07 to 0.14 per 10,000 children. Although symptomatic venous thromboembolism occurs less commonly in children compared to adults, pediatric thrombosis is being increasingly recognized as a complication of modern hospital-based care by the pediatric community.

The annual rate of venous thromboembolism in pediatric inpatients has been increasing over time.

In the seven-year period, from 2001 to 2007, the annual rate of venous thromboembolism increased by approximately 70 percent, from 34 cases to 58 cases per 10,000 pediatric hospital admissions.

In children, as with adults, the incidence of thrombosis is heavily influenced by age. In children, the peak incidence occurs in the neonatal period. After the first month of life, there is a second peak that occurs during the remainder of the first year of life, and another peak that occurs during adolescence.

Although the most common risk factor for thrombosis in pediatric patients is the presence of an indwelling central catheter, the types and distribution of thrombotic events that occur in neonates differ from those occurring in older children. However, across all age groups, venous thrombosis is much more common than arterial thrombosis.

Renal vein thrombosis occurs primarily in neonates, often in the first day of life. Portal vein thrombosis is also seen in neonates, usually in

conjunction with an umbilical catheter. In addition, cerebral sinovenous thrombosis and purpura fulminans also occur during the neonatal period. The most common type of thrombosis occurring beyond the neonatal period is deep vein thrombosis, pulmonary embolism, and cerebral sinovenous thrombosis.

One of the most striking differences between pediatric and adult thrombosis is that children generally develop thrombosis in the setting of an underlying predisposing event or risk factor, whereas in adults a number of thromboses appear to be idiopathic.

This slide lists common risk factors associated with the development of clots in children. As I mentioned, the presence of an indwelling central venous line appears to be the single most important risk factor for the development of thrombosis in childhood, although many children have multiple coexisting risk factors. For instance, the presence of a central venous line plus malignancy is a common combination of risk factors that occur in children who develop thrombosis.

Other risk factors include sepsis, surgery, congenital heart disease, use of total parenteral nutrition, trauma, inflammatory conditions such as lupus, sickle cell disease, renal disease such as nephrotic syndrome, inherited or acquired thrombophilias, medications such as L-asperaginase, and solid organ transplantation.

As with adults, children may suffer complications following treatment for a thrombosis. First, there is a risk of recurrent thrombosis in children who have developed a clot. Data from childhood thrombosis registries in the Netherlands, U.K., and Canada indicate that recurrent thrombosis occurs in between 5 and a half to 18 and a half percent of children following treatment of a clot. In addition, post-thrombotic syndrome and embolic events such as pulmonary embolism following DVT are well-known complications of thrombosis, although their incidence is not well-characterized.

Reports of mortality directly associated with thrombosis indicate that 1 to 2 percent of pediatric patients die due to complications from thrombosis.

And, finally, venous thromboembolism in the context of solid organ transplantation is a significant problem. For instance, thrombosis is a common cause of graft failure following renal transplant.

For the purposes of this meeting, we will focus on the treatment of venous thromboembolism, which is the most common type of pediatric thrombosis. Anticoagulant drugs are the primary therapy for venous thrombosis, but occasionally thrombolytic agents are also used.

In general, the choice of anticoagulant, dose intensity, and duration of therapy for thromboses in pediatric patients is based on expert consensus opinions that have been derived from extrapolation of adult data, such as the Chest Guidelines. Guidelines are also based in part on the accumulated experience of anticoagulant use in pediatric patients, as well as a limited number of published prospective studies of anticoagulants used to treat pediatric thrombosis.

The three most commonly used anticoagulants currently used in children are unfractionated heparin; the low-molecular-weight heparins, primarily

enoxaparin; and warfarin. Although these agents have been used for many years and there is a great deal of accumulated experience with their use in pediatric patients, there have been very few prospective trials of these agents, and none that have established comparative safety and efficacy for pediatric indications.

Unfractionated heparin tends to be primarily used for acute thrombosis management in hospitalized patients, especially in neonates, unstable patients, and those requiring short-term, easily reversible anticoagulation. Enoxaparin is used in infants and young children who can be maintained at stable doses and require longer-term anticoagulation. Warfarin is commonly used in older children and adolescents who require long-term anticoagulation because it can be orally administered.

One common approach to therapy of venous thromboembolism in children is treatment with unfractionated heparin or a low-molecular-weight heparin for a period of 5 to 10 days, followed by a transition to oral vitamin K antagonists, such as

warfarin, for 3 to 6 months. Of course, in addition to treatment with anticoagulants, when applicable, inciting agents such as central venous lines are removed, and any predisposing conditions that contributed to the development of the clot are treated.

There are several limitations and challenges associated with the use of unfractionated heparin, enoxaparin, and warfarin. Unfractionated heparin is intravenously administered and has unpredictable clearance and activity, especially in neonates. This may increase the risk of worsening thrombosis or bleeding in our most vulnerable patients. Therefore, frequent monitoring and dose adjustment are often required in patients treated with unfractionated heparin. Further, monitoring of activated partial thromboplastin time, or APTT, alone, may not be a reliable marker for assessing whether therapeutic levels of unfractionated heparin are being achieved and maintained.

Dosing of unfractionated heparin in children may need to be titrated based on multiple factors in

addition to APTT, including anti-Xa activity, the clinical significance of the clot, and the individual patient's bleeding risk. Because unfractionated heparin works as an anticoagulant by increasing the inhibitory effects of thrombin and factor Xa, its anticoagulant properties depend on the presence of thrombin. So in patients such as neonates that have low levels of antithrombin, it may not be as effective. In addition, it does not effectively inhibit clot-bound thrombin.

Chronic use of unfractionated heparin can also have adverse effects on bone metabolism, leading to osteopenia. And, finally, heparin use is associated with the rare but life-threatening complication of heparin-induced thrombocytopenia, or HIT.

The low-molecular-weight heparins have several advantages over unfractionated heparin, such as more stable pharmacokinetics and more predictable anticoagulant activity compared to unfractionated heparin. The low-molecular-weight heparins such as enoxaparin have a longer half-life, which allows for

outpatient use. For these reasons, it now appears that enoxaparin is more commonly used that unfractionated heparin in the initial treatment of venous thrombosis in children.

The primary disadvantage of the low-molecular-weight heparins, of course, is that they require twice-daily subcutaneous administration. It is also difficult to rapidly reverse their anticoagulant effect. The low-molecular-weight heparins also affect bone metabolism, and although the extent of this effect has not been well-studied, its use for several months may adversely impact bone development. Finally, the low-molecular-weight heparins are also rarely associated with the development of HIT.

As I mentioned earlier, the main advantage of warfarin is that it is orally administered. Warfarin's long half-life allows for once-daily dosing, and administration of vitamin K can rapidly reverse its anticoagulant effects. However, it is very challenging to use because it is a narrow therapeutic index, which confers both an increased

risk of bleeding complications as well as a risk of inadequate anticoagulation.

The anticoagulant effect of warfarin is greatly affected by the vitamin K content of the diet, and there are drug interactions with warfarin that can affect its activity. For example, the use of antibiotics, which is common in children, can effect the INR achieved by a given warfarin dose.

Because of the narrow therapeutic index and potential for alterations in anticoagulant activity due to changes in medication and diet, patients on warfarin therapy must have frequent blood tests to monitor INR. Warfarin also comes only in tablet form, so it has a limited usefulness in infants and young children.

Aside from the limitations and difficulties associated with the use of heparin agents and vitamin K antagonists, there are other challenges to the treatment of thromboses that are particularly relevant to pediatrics. As I mentioned earlier, due to a lack of well-controlled anticoagulation trials in pediatric patients, pediatricians generally rely

on expert consensus guidelines that are based on adult data.

Although these guidelines are extensively used, they are based on a relatively low level of evidence and generally do not address the use of newer anticoagulants. Children are treated off-label with anticoagulants approved for the treatment or prevention of thrombosis in adults. However, the extent to which we can rely on adult data to guide dosing and choice of anticoagulants to treat thrombosis in pediatric patients is uncertain.

First, as I mentioned earlier, the underlying pathophysiology of pediatric thrombosis may be different in children. Second, a child's predisposition for development or worsening of a clot may vary over time, depending on the child's clinical condition.

In addition, the optimal treatment of clots occurring in children require a more tailored approach due to the normal developmental alterations in hemostasis, metabolism, diet, body weight, level of physical activity, and behavioral maturity that

occur throughout childhood.

Treatment of pediatric patients is also hampered by the lack of pediatric formulations. As I mentioned, warfarin is only available in pill form, and the low-molecular-weight heparins are subcutaneously administered. Finally, further study is needed to define the role of anticoagulants in the prophylaxis of thrombosis in children.

There are 11 anticoagulants that are currently approved and marketed in the United States for the treatment of prophylaxis of thromboses in adult patients. Of these, there are several new agents that have the potential to provide a meaningful advance in the effective and safe treatment of children who have thrombosis. Each of these drugs offer potential advantages over the more commonly used anticoagulants in children.

Some of the new agents, such as the direct thrombin inhibitors, have a mechanism of action that differs from that of traditionally used agents. And most, if not all, of the newer agents also appear to have a more predictable pharmacokinetic and

pharmacodynamic profile in adults compared to unfractionated heparin and warfarin, and a few can be orally administered.

The direct thrombin inhibitors have several potential advantages over the commonly used agents in kids. They do not require the presence of antithrombin because they bind directly to thrombin, and therefore may be particularly beneficial in children, such as neonates and critically ill patients, who have low levels of antithrombin.

Unlike heparin, they can also inactivate clot-bound thrombin. They also have predictable pharmacokinetics and may have less bleeding potential compared to unfractionated heparin. Finally, they also have a role in the treatment of patients who develop HIT.

Three intravenously administered direct thrombin inhibitors have been used in children: argatroban, bivalirudin, and lepirudin. Argatroban and bivalirudin have been prospectively studied, but there is still limited data available on their use in children. Argatroban labeling currently contains

dosing recommendations for the treatment of pediatric patients with HIT, but this information is prefaced by a statement that the safety and effectiveness of argatroban have not been established in pediatric patients.

Dabigatran is an oral direct thrombin inhibitor that is currently approved for use in adults. There are currently two open label single-arm studies of dabigatran underway to characterize the pharmacokinetics, pharmacodynamic activity, and safety of its short-term use in children.

Fondaparinux is a synthetic factor Xa inhibitor that is chemically related to the low-molecular-weight heparins. However, it offers potential advantages over the low-molecular-weight heparins currently used in children, such as once-daily subcutaneous dosing and a lower risk of heparin-induced thrombocytopenia. One single-arm dose-finding study of fondaparinux in 24 pediatric patients over the age of 1 year has recently been completed.

Finally, rivaroxaban is an orally

administered direct factor Xa inhibitor for which there is currently one open-label, single-dose study in children.

As some of the upcoming presentations will describe in more detail, several of these newer agents have been studied, or are in the process of being studied, in small, open-label, single-arm studies in children. However, most of these studies are limited by the small number of patients enrolled and are generally designed to characterize the pharmacokinetic and pharmacodynamic activity of the anticoagulant and to evaluate the safety of short-term use rather than gather information to establish efficacy and safety of long-term use in pediatric patients.

In summary, although a few of the 11 anticoagulants that are currently approved for use in adults contain pediatric dosing information, none are approved for use in pediatric patients. The approach to treatment of thromboses in pediatric patients is based on a complex set of factors, including patient age, underlying risk factors for thrombosis, and

clinical condition. There are known limitations and risks associated with the commonly-used anticoagulants.

Because data derived from studies of anticoagulants in adults are not necessarily directly applicable to pediatric patients, there is a pressing need for additional studies that provide the information necessary to support indications and dosing recommendations for pediatric labeling of the newer anticoagulants that may provide a better safety and efficacy profile in the treatment of pediatric thromboses.

Thank you for your attention. Next, Dr. Kathy Robie Suh will present the regulatory perspective on the development of anticoagulants in children.

FDA Presentation - Kathy Robie Suh

DR. ROBIE SUH: Good morning. My name is Kathy Robie Sue. I am a medical team leader in the Division of Hematology Products here at FDA. I will present the regulatory background for today's discussion.

This slide shows an outline of my presentation. First, I will summarize key events in the regulatory history of provisions for pediatric labeling of drugs. Next, I will review the pediatric labeling history for unfractionated heparin sodium and warfarin sodium, the two oldest marketed anticoagulants. Then I will briefly describe the indications and the current pediatric labeling for the approved marketed anticoagulant products.

Finally, I will delineate some of the issues that have arisen as the division has attempted to apply the current regulations to stimulate studies in order to provide additional information for use of these drugs in pediatric patients. I will end with a few summary conclusions.

The pediatric use section was added to the package insert in 1979 as a subsection under precautions. To add information to this new section, adequate and well-controlled studies were required. Rather than do these studies, most manufacturers simply added some variant of a disclaimer that safety and effectiveness in pediatric patients had not been

studied.

In 1994, the pediatric rule was passed. This rule required manufacturers of marketed drug and biological products to survey the existing data and determine whether those data were sufficient to support additional pediatric use information in the drug's labeling. It provided for extrapolation of use in adult patients to pediatric patients if extrapolation could be justified, based on sufficient similarity in the adult and pediatric populations, of the course of the disease and the effects of the drug, both beneficial and adverse.

While this rule did result in some labeling revisions for older drugs, for most drugs, manufacturers simply concluded that no changes were warranted, and they revised the wording of the disclaimer to comply with the rule.

In 1997, the FDA Modernization Act, FDAMA, was passed. FDAMA provided manufacturers with an incentive of an additional six months of patent protection, referred to as pediatric exclusivity, for products where needed pediatric studies were

voluntarily done in response to a written request from the FDA. Then in 1998, the pediatric final rule was passed, requiring pediatric studies of certain new and marketed drug and biological products.

In 2002, most of the provisions of the 1997 law were included in the Best Pharmaceuticals for Children Act, or BPCA. And in 2003, most of the provisions of the 1998 law were included in the Pediatric Research Equity Act, or PREA. Both BPCA and PREA were reauthorized in 2007 in the Food and Drug Administration amendments of that year. Currently, BPCA and PREA are the two rules that most directly address development of drugs for use in pediatric patients.

These next two slides describe some of the main features of PREA and BPCA. Major features of PREA are shown here. Pediatric studies are required for a drug when there is a submission for a new active ingredient, a new indication, dosage form, dosing regimen, or route of administration.

The studies must assess safety and effectiveness of the drug or biological product for

the claimed indication in all relevant pediatric subpopulations. It must use age-appropriate formulations, and must include data to support dosing and administration. FDA may grant deferrals or waivers of certain required studies, if appropriate.

Major features of the BPCA are shown in this slide. The BPCA grants six months of additional exclusivity, pediatric exclusivity, in return for sponsors voluntarily conducting and submitting FDA-requested pediatric studies that are contained in a written request.

In the BPCA process, the FDA determines if there is a public health need for pediatric studies and issues a written request, if appropriate. The manufacturer receives the additional exclusivity if the studies submitted fairly respond to the written request and are conducted within specified time frames indicated in the letter. When a manufacturer receives a written request, that manufacturer must incident to the agency within 180 days of their intent, or not, to perform the studies.

As examples of how legislation has affected

labeling of anticoagulant drug products for use in pediatric patients, in these next several slides, I will show the uses and pediatric labeling history for the two oldest anticoagulant products, unfractionated heparin sodium and warfarin sodium.

Heparin was first approved in the United States in 1939. This slide shows the current approved clinical indications for unfractionated heparin. Important for our discussion today is the first listed indication, namely, prophylaxis and treatment of venous thrombosis and pulmonary embolism.

Following introduction of the pediatric use section in 1979 and continuing to 2011, the pediatric use section of the label for heparin referenced the dosage and administration section. In the dosage and administration section, dosing recommendations were made for children, referring to appropriate pediatric reference texts. No treatment durations or limits for pediatric patients were included in the recommendations. The 1994 pediatric rule did not evoke any changes in this information.

After passage of the pediatric exclusivity provisions in 1997 and continuing to the present, there was no effort on the part of manufacturers to obtain a written request for pediatric studies from the agency. Also, since implementation of PREA provisions, there have been no NDA supplements submitted. which have triggered the PREA requirement for pediatric studies for heparin.

This slide summarizes the most recently approved pediatric use section for a heparin sodium product. This happens to be a new unfractionated heparin product, NDA, that was approved July 21, 2011. This label clearly states that there are no adequate and well-controlled studies of heparin in pediatric patients, and indicates that the recommendations provided for pediatric use are based on clinical experience. Practitioners are still referred to the dosage and administration section for dosing.

In the dosage and administration section of the heparin label, mention of referenced texts was removed from the label. In the absence of adequate

and well-controlled studies in pediatric patients, the dosing recommendations remained based on clinical experience and generally are in keeping with current practice guidelines.

Warfarin sodium was first approved in the United States in 1954. It is approved for the indications shown in this slide. Again, importantly for today's discussion is the broad anticoagulation indication for prophylaxis and treatment of venous thrombosis and pulmonary embolism.

From the introduction of the pediatric use section in the label to 1996, the warfarin label included the disclaimer that, "Safety and effectiveness in children below the age of 18 have not been established."

In response to the 1994 pediatric rule, the label was updated to include some information about use in pediatric patients, as shown in this slide. The revision acknowledged experience with using warfarin in children, but also cautioned regarding difficulty of achieving and maintaining therapeutic INR ranges in pediatric patients.

Very recently, a supplement was approved to update the label for Coumadin in response to the physicians labeling rule, and the wording of the pediatric use information in the labeling was revised to clearly indicate that pediatric use is based on adult data, mainly, and recommendations.

The pediatric use section also elaborates upon the variability seen in pediatric patients, particularly cautioning that the developing hemostatic system in infants and children results in a changing physiology of thrombosis and response to anticoagulants, and it cautions regarding possible interactions with infant formulas.

This slide shows the currently approved and marketed parenterally administered anticoagulant products. The drugs highlighted in yellow are approved generally for venous thromboembolism treatment in adult patients. The dosing for these drugs calls for treatment with the parenteral drug for several days while administration of warfarin is begun and until INR values are in the therapeutic range.

For the newer agents, the low-molecular-weight heparins and Arixtra, the treatment duration in the adult studies is generally in the range of 7 to 10 days. There are no studies or labeling to support use of any of these agents for VTE treatment during the full duration of 3 to 6 months recommended for treatment of venous thromboembolism.

With the exception of unfractionated heparin, all of these drug products carry a disclaimer in the pediatric use section of the labeling, stating that safety and effectiveness of the drug in pediatric patients have not been established.

This slide shows the currently approved and marketed orally administered anticoagulant products. Only warfarin is currently approved for treatment of VTE. Dosing calls for overlapping treatment with parenteral anticoagulant until INR levels are therapeutic. Both Pradaxa and Xarelto carry a disclaimer in the pediatric use section of the labeling, stating that safety and effectiveness of the drug in pediatric patients have not been established.

In working to develop written requests for pediatric studies under BPCA and requirements for pediatric studies under PREA for venous thromboembolism treatment with anticoagulant drug products, two particular aspects of the adult drug development programs for VTE treatment have been found to be problematic for the pediatric population.

First, use of parenteral anticoagulants in VTE treatment is approved in conjunction with warfarin, with oral warfarin being started usually within 72 hours and with duration of parenteral anticoagulation of about 7 days, 5 days minimum, until the INR is in the therapeutic range. This specific use of the parenteral agent in conjunction with warfarin may be problematic, particularly in young pediatric patients. Second, there are no submitted adequate and well-controlled clinical trials with the use of a single parenteral anticoagulant for the entire duration of VTE treatment.

Additional considerations for studies in pediatric patients that have been identified, and

some of these have already been discussed by Dr. Donoghue, are listed in this slide. These include, that developmental aspects of anticoagulation may play a role in dosing and response; there are special safety concerns in pediatrics, such as bone development; there is a need for additional safety information beyond the initial 5- to 7-day treatment period for the newer agents; clinical setting profile for the adult studies may not adequately reflect the clinical setting profile for pediatric use. Finally, there is no clearly established quantitative relationship between degree of anticoagulation or blood activity levels, such as anti-Xa levels and clinical outcome.

Considering the issues and factors noted in the previous slide, written requests issued for anticoagulants for VTE treatment have included elements as listed in this slide. Among these are that pharmacokinetic and pharmacodynamic data are needed for the entire age range, birth to 16 years; that there is a need for a randomized, controlled safety and efficacy study with the parenteral agent

in conjunction with warfarin in pediatric patients, reflecting the adult studies; study endpoints that should be incorporated in the study should include pharmacokinetic and pharmacodynamic parameters such as anti-factor Xa, antithrombin, activated partial thromboplastin time; clinical efficacy endpoints of recurrent VTE, bleeding, and transfusion; clinical safety endpoints, hemoglobin, hematocrit, and bone development.

Thus far, we have not had a submission of pediatric studies for any anticoagulant to substantively address these elements.

In conclusion, at the present time, with regard to investigation of anticoagulants for use in pediatric patients, we conclude the following:

Use of anticoagulants in pediatric patients largely is driven by clinical experience in adults in the absence of labeling based on adequate and well-controlled studies in pediatric patients.

Commercial development of anticoagulant drugs typically addresses thromboprophylactic indications before VTE treatment indications.

Some aspects of the use of newer drugs, such as the low-molecular-weight heparins, for treatment of DVT/PE in adults appear problematic in children; for example, the transition from parenteral low-molecular-weight heparin to warfarin.

The approach to product development for anticoagulants is sufficiently variable among manufacturers such that it is difficult to devise a standard or cohesive approach to obtaining pediatric information for these drugs that can be applied across the therapeutic drug group.

Finally, the areas of greatest need for pediatric study of anticoagulants need to be clarified.

In light of these conclusions, we are seeking today the committee's advice to determine a path forward for addressing needs for use of these anticoagulant agents in pediatric patients.

Now Dr. Snyder will present results of an exploratory survey directed to pediatric hematologists on this subject. Thank you for your attention.

Clarifying Questions from Subcommittee

DR. BALIS: Why don't we see if the panel has any questions for the first two presenters before Dr. Snyder presents. And while people are thinking about that, we had two members join the panel since we introduced ourselves. So Dr. Minniti and Dr. Young, could you introduce yourselves, please?

DR. MINNITI: Yes. I'm Caterina Minniti. I'm --

DR. BALIS: Push your red button. Push the button there. Yes.

DR. MINNITI: I'm Caterina Minniti. I'm a pediatric hematologist/oncologist currently working in the intramural NHLBI division on the main campus at NIH.

DR. YOUNG: And I'm Guy Young. I'm a pediatric hematologist from Children's Hospital Los Angeles. I apologize for coming in a couple minutes late; I forgot, after living on the east coast for all these years, that meetings actually start on time. In California, nothing ever starts --

[Laughter.]

DR. YOUNG: No, I'm not kidding. Nothing ever starts right on time. So apologies for that.

Actually, I do have one question.

DR. BALIS: Yes, please.

DR. YOUNG: Dr Robie Suh, you stated -- and I'm aware of a lot of the guidance from the FDA, about that pediatric studies go up to the age of 16, and then adult studies start at the age of 18. So what happens to the 16- to 18-year-olds? I mean, in my studies, I've always included children up to 18. So there's a gap there, and I wonder why that exists and if that can be closed.

DR. ROBIE SUH: Actually, I think when we -- back to the 1994 rule, I believe they worked on breaking down the pediatric age ranges, and it went up to the -- ended up going up to the 16th birthday. And so the 16th birthday and above were considered part of the adult population.

I think we realize, of course, the legal things that you have to deal with, that they're still pediatric patients for the purpose of getting consent and that sort of thing, and assent. But based on the

determination that was made very broadly, that the 16th birthday was physiologically a good break point between pediatrics and adults.

I think in saying that, for any particular drug, the age ranges that are investigated may be tailored, and it is not uncommon to include patients up to the age of 18 in the adolescent age range for pediatric studies.

DR. YOUNG: Yes. I just think it's important to point out that when the manufacturers do studies in adults, that starts at 18. And so if you're only going to require studies to be done for children up to 16, for example, in written requests or things like that, then we're left with a gap. And I think that we should try not to have that gap.

DR. DURMOWICZ: Just to add on to what --

DR. BALIS: Oh, I'm sorry. Go ahead.

DR. DURMOWICZ: I'm sorry. To add on to what Kathy said, the age range for pediatric patients was outlined in the legislation, so up to less than 17. So we acknowledge there was a gap there.

DR. BALIS: Dr. Freedman?

DR. FREEDMAN: I have two questions. Do we know why the frequency of VTE in the pediatric population is increasing? Is it related to procedures or to pathophysiology? That's my one question. And maybe we could deal with that first.

DR. BALIS: Dr. Donoghue, do you want to address that?

DR. DONOGHUE: I'm sure he knows more than I do.

I think the general impression is that it may partially relate to the increase in interventions that are now occurring, increased used of central lines, better awareness of thrombosis, better imaging techniques, things like that.

DR. FREEDMAN: Surgical procedures or --

DR. DONOGHUE: I'm sorry?

DR. FREEDMAN: Surgical procedures?

DR. DONOGHUE: Yes. I think it's a combination of all of the above. I think as we become more sophisticated medically and the procedures that children undergo become more complicated and more common, I think as a result we

see more predisposition for the development of clots.

DR. FREEDMAN: So that would seem to be a good target population for future studies.

DR. BALIS: Dr. Shearer?

DR. SHEARER: To follow up on what Dr. Young articulated, I, too, think it's very important to extend the age range for pediatric studies in anticoagulation, particularly since, in the oncology domain, in which many if not most of us practice, the age of pediatric protocols now extends up to age 30 for many leukemia and solid tumor trials. And those of us who see these patients in the academic setting are getting referrals of patients who are enrolled on therapeutic trials through COG who are well over the age of 17 or 18.

So I think that for a number of reasons, we do need to look carefully at the age of inclusion of participants in pediatric studies for anticoagulation.

DR. BALIS: Thank you.

Dr. Freedman, did you have another question? I'm sorry. I cut you off.

DR. FREEDMAN: Yes. I had another question. And I was just wondering, since several drugs have been recently approved since -- well, in the last 10 years, say, I wondered whether the PREA and the BPCA have been applied there. In other words, have those companies been required to put a plan in place, or is there a plan in place for them to do studies on pediatric patients? And if not, were they granted waivers, or why was that not done?

DR. ROBIE SUH: We can say for -- written request letters that are issued are not public, but we can say what they've been issued for, that there has been a letter issued for Lovenox. There was one for argatroban, and one for bivalirudin. And I summarized, I think, in one of my slides some of the general elements of the sorts of things that we ask for in those studies.

Argatroban's manufacturer attempted to do some studies and submitted some information. And as Dr. Donoghue said, some information was included in the label for safety reasons because there were found to be problems with some of the dosing, increased

bleeding in certain patients receiving the drug, young infants.

For the other written requests that have been issued, we have not received -- as I stated, we have not received studies that have been completed in response to those written requests.

DR. FREEDMAN: It seems that the requests become somewhat voluntary, the response. In other words, it seems like the responses may be some voluntary. In other words, you request the companies to look into doing the studies, but there doesn't seem to be necessarily a follow-through to ensure that they are done. It's just a question of how the regulation is applied, and that's what I'm not sure about. I don't understand how it's been applied.

DR. ROBIE SUH: Absolutely. The written request process, the BPCA process, that process is voluntary. And, historically, we do not hold the approval for the adult indications hostage, if you will, to the studies in pediatric patients. And it may be that within the practice community for pediatrics, physicians are accustomed to not having a

lot of dosing information to directly direct pediatric dosing and have learned, over time, how to use certain agents. So, yes, the exclusivity requirements are -- doing those is a voluntary thing.

The PREA, on the other hand, is a required thing, with approval of a supplement. But for most agents, the newer agents that have come in with prophylactic indications, typically in major orthopedic surgery, elective hip replacement, elective knee replacement, that for those indications are not really directly applicable to a substantial pediatric population. So those studies are not required in that context.

DR. BALIS: Dr. Reaman, did you have something to add to that?

DR. REAMAN: I was just going to talk about the voluntary nature, but I think Dr. Robie Suh covered that.

DR. BALIS: Okay. She did, very well.

DR. REAMAN: There really is no mechanism for follow through. I mean, it's basically a voluntary program, and it's really up to the sponsor to decide

whether they want to perform the studies, or if they begin the studies, to continue the studies.

DR. BALIS: Thanks.

Dr. Luban?

DR. LUBAN: I'd just like to make one point to Dr. Freedman, and that is that when we start talking about VTE -- and Kristen may go into this -- there's spontaneous VTE and then there is the medically and surgically fragile child with VTE. And we really do have to keep those two populations separate. And when you get to the medically and surgically fragile child, we also have to make sure that we consider the premature infant.

One question that I have for FDA is, has anybody done any studies or evaluation of the amount of heparin that's administered for prophylaxis against VTE by keeping lines open in any population? Because many, many fragile infants, and particularly prematures, are totally supported with intravenous lines, umbilical lines, central venous lines, that are cleared with heparin regularly. And the cumulative effect of that heparin has never really

been evaluated, to my knowledge, but you may know more than I do.

DR. FARRELL: I would tend to agree with your comment, that there really isn't a lot of accumulated data on that.

DR. BALIS: Dr. Shurin?

DR. SHURIN: Yes. I think that what Dr. Luban just said, I think, emphasizes -- as we did yesterday, we have tremendous heterogeneity in the underlying problem. So you have the variable of age, but you also have the variability of the underlying diseases.

So spontaneous thrombosis in a child is much more likely to be related to an inherited disorder than it is in an adult. And so you not only have the complications of the underlying problems, but you also have the fact that you may have children who are going to be on these drugs lifelong or for very long periods of time, which is not necessarily the case for many older people.

So looking -- I think the heterogeneity makes all of this incredibly complicated. You look at the

underlying indication, and venous thromboembolism on the basis of -- a post-surgical venous thromboembolism is a lot different from something that's on the basis of protein C deficiency or something.

So I think in terms of -- we just sort of need to keep many of those things in mind as we're having the rest of these discussions because the categories that we usually use for adults don't apply in the same way in children; they're so much more heterogeneous.

DR. BALIS: Thank you.

Yes, Dr. Durmowicz?

DR. DURMOWICZ: I just want to add a little bit on to some of the regulatory teeth that we have in the process. We do have three drugs that have PREA requirements outstanding. As Kathy said, we needed to waive the PREA requirements for some drugs because the indication really was not common enough in pediatric patients for studies to be feasible.

But dalteparin, fondaparinux, and tinzaparin all three do have PREA requirements to study their

drugs. For dalteparin, it's actually in pediatric cancer patients for treatment of VTE. And then in fondaparinux and tinzaparin, it's a treatment indication for DVT and PE in conjunction with warfarin, which is difficult.

The additional leverage we have through the Best Pharmaceuticals for Children Act is the ability to study off-patent drugs or products that at least have one patent that's expired. And NIH is actually working right now with a group of experts, a hematology working group, to help identify therapeutic gaps in pediatric hematology, pediatric therapeutics.

DR. BALIS: Dr. Kaskel?

[Technical difficulties with microphone.]

DR. KASKEL: I just wanted to mention in a certain population in renal disease, the children have to go (inaudible). So puberty starts later and will affect the age of its transition. And also, about 20 percent of the children and adolescents receiving replacement therapy would be out of that 17, which would take care of a lot of young adults up

to 21 with the products and with risks.

So I think we have to readdress the age limit here.

DR. BALIS: Thank you. Those microphones really aren't working very well.

For clarity from the FDA, the goal, the overall goal of these studies, I assume, is both to improve the pediatric labeling. But are we also looking for studies that would result in a licensed indication in a pediatric population from these studies? What's the goal of pursuing this line of study?

DR. FARRELL: Well, ideally, an indication would be nice. But practically speaking, I think we'd like to get some information into the labeling. So, yes, we would be willing to grant an indication if there was a sufficient body of evidence. But I think that we'd be interested in getting our pediatric written requests completed such that we could put something in labeling to guide dosing.

DR. BALIS: Okay. Other questions? Yes, Dr. Sekeres?

DR. SEKERES: We saw the incidence rates of thromboembolic events in kids. General number, I'm used to seeing things per 100,000, not per 10,000.

So how many per year in the U.S.?

DR. DONOGHUE: I don't think I ever heard it expressed in the number of kids per year. And the reason it was expressed per 10,000 is because it's such a small rate to begin with. So I think the number I quoted was .07 per 10,000 children. I can work on the numbers and give you a harder number if you want that.

DR. SEKERES: Okay. The --

DR. YOUNG: Can I add something to this? So I think it's just not known, to be honest with you. And the CDC has recently had some initiative to try to identify that. Unfortunately, they don't have the funding to support the grants that were submitted.

But I honestly don't think it's known. The numbers that you see quoted in the literature, I mean, the most recent numbers from Dr. Raffini's study that were demonstrated indicate that it's about 58 per 10,000. So I guess you'd say 580 per 100,000.

But those are hospital admissions, right? Oh, yes, 5.8. Sorry. So those are hospital admissions, so those are inpatients.

I think, just to follow on from what Dr. Shurin said, is that the vast majority of children that get thrombosis either get them as an inpatient or as a result of catheters or procedures or things like that. There is a not small minority of patients that do develop a VTE just idiopathically, like adults do, but that's the smaller proportion.

But I think, really, we don't really know what the number is. I think when the academics all look at these numbers, and then we talk about our own practices, you know, we can't believe that the numbers are really that small. I think that the numbers are a lot higher, and it's just not known.

DR. SEKERES: So the reason I ask is not to drill you about statistics, but to try to figure out what type of trial you could really design. If there's really such a paucity of kids out there who are getting these events, you probably couldn't have

any kind of dedicated randomized study as we do in adults. You'd probably have to be -- I'm guessing, if it's really this small, require that adult trials just enroll kids also so you get some sort of safety and efficacy experience.

Is that your impression also, or, no, you think there are enough out there that you could a well-designed study?

DR. FARRELL: Usually, when the first indication comes in for VTE, it's usually for orthopedic hip or knee surgery. And so it would usually preclude enrollment of children. Even though that occurs, we'd still like to get a small trial in pediatrics because we know it won't be used for that indication but for other uses.

DR. BALIS: Dr. Reaman?

DR. REAMAN: And I think you'll probably hear some information from sort of an informal survey or questionnaire of institutions. I think the numbers probably do exist, and many of the studies that we do in the pediatric population are smaller than adult trials. But I think there's more than

just a subtle indication that there are sufficient patients to do trials. What's lacking to support those trials you'll hear about also.

But I don't think numbers are really the issue. The problem is the heterogeneity and whether these are spontaneous thromboses or intervention- or disease-related thromboembolic complications. But I think even within those subpopulations, there's ample opportunity, as far as patient numbers, to do controlled clinical trials.

DR. SEKERES: So I agree with you. But I do think numbers are going to play a role in this. I mean, the adult trials enroll thousands of people to be adequately powered to find some small difference they're hoping will get their approval. I think with kids, it's going to have to be more along the lines of how we approach rare cancers to do those sorts of trials.

DR. DONOGHUE: I have something else.

DR. BALIS: Oh, yes.

DR. DONOGHUE: I have something else to add. I think that's one reason why we're having this

meeting, is because we do know there are challenges due to small numbers. And I think the challenges are even more accentuated when you're looking at prophylaxis indications in children as opposed to looking at studying treatment for thrombosis.

But Dr. Ronald Portman is here, and he is from Bristol-Myers Squibb. And he's done his homework better than I have. He has some better numbers that he can give you. And he'll also be presenting a little bit later today.

So Dr. Portman?

DR. PORTMAN: It's just gratuitous that a paper came out this week from Cetti, et al., and they basically reported 188 patients with VTE per 100,000 discharges in children's hospitals. So that's the latest figure that we have, which is not really inconsistent with Leslie Raffini's studies.

Greg, I'm going to remember you said there's not going to be patient number problems. I'll remember that.

DR. BALIS: Can you say your name for the record, sir?

DR. PORTMAN: I'm sorry. Ronald Portman.

DR. SEKERES: Sorry. I still think it's going to be challenging to figure out these numbers because, again, we don't think of this in terms of hospital discharges. We think of incidence rates per year in the U.S. for cancers and hematologic conditions. I still don't know what that number means in terms of patient enrollment.

DR. BALIS: Thank you, Dr. Sekeres.

Dr. Shurin?

DR. SHURIN: I'd like to underscore what Dr. Young said about sort of underreporting. It's not a reportable disease. For many of the kids who are medically fragile, it's the least of their problems, of the kids in the newborn nursery who go home. Many of the oncology patients, when they come back years later, you see the collaterals, which is the only way you actually know that there was a clot around the central line that was in for two and a half years.

I think if there were available studies, the importance of identifying these patients and coming

forward with this would actually be recognized very, very rapidly.

DR. BALIS: Thank you.

Yes, Dr. Robie Suh?

DR. ROBIE SUH: I just wanted to make just one comment about the older adolescents, enrolling patients 16 to 18 years. That's generally not a problem with the studies that we ask for. I think the concern is that you not end up with all of the adolescents being 16 to 18 and not having any 12- or 13- or 14-year-olds. But in terms of the practical writing of a protocol, that's not a problem.

DR. BALIS: Thank you.

Let's proceed on to another presentation from the FDA. And, Dr. Snyder, you can introduce yourself, too, please.

FDA Presentation - Kristen Snyder

DR. SNYDER: Good morning. My name is Kristen Snyder, and today I will be presenting general perspectives from academia and industry regarding the use and development of anticoagulant products in the pediatric population.

As part of our preparations for this pediatric subcommittee of the ODAC meeting, we determined that to better understand the challenges of developing anticoagulant drugs for the pediatric population, we needed to gather input from the pediatric medical community and from industry. In order to do so, we conducted very informal telephone interviews with both members of academia and industry who have experience relevant to this topic.

My colleagues, Dr. Martha Donoghue and Dr. Greg Reaman and I would first like to thank all those who agreed to share their perspectives with us. We are hopeful these discussions will promote improvements in anticoagulant drug development for the pediatric population.

Interviews were conducted by telephone by three medical officers from the Office of Hematology and Oncology Products. Interviewees included both industry and academic members of the pediatric medical community. All interviewees were notified that the results of these discussions would be pooled, kept anonymous, and discussed publicly.

Before providing results of our discussions with academia and industry members, I would like to first note that these results represent a very small sampling of pediatric subspecialists, institutions, and companies who we selected based on our knowledge of their subspecialty or their known involvement in developing an anticoagulant product. It is meant to provide a starting point for discussion of anticoagulant drug development and potential challenges seen by stakeholders in academia and industry. It does not reflect the position of the agency.

I will begin by giving an overview of those interviewed, and proceed with results of our discussions with academia, followed by those with members of industry. Because our questions were directed specifically for each group, they will be discussed separately.

Twenty-seven physicians from academia whose subspecialty field was likely to treat patients at risk of thromboembolism, and 12 industry members whose companies have known involvement with

development of an anticoagulant product, were initially contacted by phone or email to participate in a general discussion of anticoagulants. Attempts were made to replace pediatric subspecialists who did not respond with a specialist in the same field. Industry members could not be replaced.

Those eventually interviewed included 22 pediatric subspecialists, 19 of whom practice at children's hospitals, two in hospitals with dedicated pediatric units, and one who practices in an outpatient clinic affiliated with a major medical center. Six members of industry were also interviewed.

All members of academia interviewed were initially asked about their experience prescribing anticoagulants. All 22 physicians interviewed prescribe anticoagulants to their pediatric population. All non-hematology subspecialists interviewed prescribed anticoagulants in consultation with pediatric hematology subspecialists.

The most common diagnoses requiring anticoagulation seen in practice by our interviewees

included deep venous thrombosis, seen by 95 percent of those interviewed; ischemic stroke, seen by 73 percent; pulmonary embolism, seen by 64 percent, while 9 percent of those interviewed prescribe anticoagulants as prophylaxis for catheter-related thrombosis.

Other indications for which pediatric subspecialists prescribe anticoagulants include treatment of intracardiac thromboses following cardiac surgery, graft failure in transplant patients after anastomoses, extracorporeal membrane oxygenation circuit clotting, arterial thromboses, and primary prophylaxis in high-risk populations, such as those patients with known thrombophilias undergoing immobilizing surgery or those at high-risk of recurrent stroke.

Ninety-five percent of pediatric subspecialists interviewed stated that they typically prescribe low-molecular-weight heparins and primarily enoxaparin, followed by 77 percent who prescribe warfarin sodium and 64 percent who prescribe unfractionated heparin. Other parenteral

anticoagulants and other oral anticoagulants are also prescribed.

Those who said they did not prescribe other oral anticoagulants stated that this was because there was not enough information for pediatric use at this time or that there was no indication for a deep venous thrombosis treatment, and therefore dose for this indication is unknown.

Because there is so little available data in labeling regarding the dose and duration of anticoagulants in children for the treatment of thromboses, we inquired how interviewees select the dose and duration of treatment.

Non-hematology subspecialists all stated they do so in consultation with pediatric hematologists. Pediatric hematologists interviewed stated that they utilized the chest guidelines with modifications for children; literature from Dr. Maureen Andrews and colleagues; standardized institutional protocols based on chest guidelines and the work of Dr. Andrews; extrapolation from the adult literature; data from the small number of pediatric studies

published; and clinical experience, where decisions are often made on an individual basis and based on assessments of ongoing risk.

Ten pediatric hematologists provided a very rough estimate of the numbers of new diagnoses of thromboses seen in their institutions yearly. These rough estimates ranged from 20 to 180 new diagnoses per year, and are seen here as the blue bars. Of those 10 institutions, seven pediatric hematologists were able to provide very rough estimates of thromboses diagnosed in the newborn or neonatal time period at their institution yearly.

The estimated number of all-new diagnoses of thrombosis seen in the neonatal or newborn period at each of the seven institutions are seen here as yellow bars. Of note, estimates for neonatal or newborn thromboses ranged from zero to 50 percent of the total new diagnoses for each of the institutions.

We also attempted to gather information regarding clinical trial experience. We first inquired as to the institutions' experience in conducting any clinical trial studying a nonmalignant

hematologic indication such as thrombosis, hemophilia, sickle cell disease, or immune thrombocytopenic purpura.

Twelve interviewees were familiar with hematology trials of some kind being conducted at their institution. Four interviewees report knowledge of either a currently open trial investigating an anticoagulant or thrombosis in the pediatric population, or a similar trial in the process of opening. None of the non-hematology subspecialists were aware of any anticoagulant treatment or thrombosis trial being conducted in pediatric patients at their institution or elsewhere.

Ten interviewees are currently or were previously an investigator on a trial investigating anticoagulants in the pediatric population. All 10 enrolled patients. Four investigators participated in trials which were terminated early. Reasons for early trial termination included termination by the company sponsoring the trial; difficulty accruing patients due to the requirements of the patient, such as increased blood draws or the

requirement for two intravenous lines; and increased serious adverse events observed. Three investigators participated in trials which were completed.

Eleven of 22 investigators were aware of successfully completed trials investigating anticoagulant products in the pediatric population. Eight interviewees cited investigator interest, seven identified funding, and four identified a collaborative consortium as well as infrastructure and a dedicated staff as the keys to the successful trials.

Other reasons cited for successful trials included feasibility of the protocol, institution size, having a commercial sponsor, appropriate and effective training for participating investigators and research nurses, study design, and concrete benefit to the patient for their participation; for instance, offering a better quality of life.

In our discussions, interviewees noted a variety of issues making the conduct of trials investigating anticoagulants in the pediatric population a challenge. These have been categorized

into the following: challenges related to the logistics of running a clinical trial, challenges related to the partnership between industry and academia, and challenges unique to the pediatric population at risk of thrombosis.

Ninety-one percent of those interviewed felt that there were challenges to conducting trials investigating anticoagulant agents in pediatrics. Challenges discussed by the interviewees related to the logistics of the clinical trial included funding, mentioned by 73 percent, and data management, staffing issues, and costs, cited by 41 percent. Eighteen percent felt it was too difficult to run a trial at their institution, and 14 percent felt they had enough patients diagnosed with thromboses, but they did not hear of them in a timely manner to enroll them.

Other logistical challenges related to the conduct of the clinical trials cited by those interviewed included the numerous institutional requirements of contracts, budgets, and pediatric research units; technical aspects of proper specimen

collection; communication efforts among trial participants; difficulties of getting an institutional research board to approve an industry-designed research protocol in pediatrics; and difficulties in powering a treatment trial in pediatric thrombosis.

Challenges discussed by the interviewees related to the industry/academic partnership included having never been approached by industry from 27 percent of those interviewed, and similarly, 23 percent stating that industry was not interested in opening a trial at their institution. Other challenges included the scrutiny surrounding an industry/academic dependence, which may lead to the appearance of conflicts of interest. Some interviewees also cited that industry may need to be willing to open trials at more sites to enable full accrual.

Challenges discussed by the interviewees unique to the pediatric population at risk for thrombosis included 18 percent of those interviewed, indicating that other competing trials of

thrombolysis agents versus anticoagulants made accrual challenging. In addition, the conditions under which thrombosis occurs in children is under different circumstances than those for adults. In the majority of cases, thrombosis is not the patient's primary medical problem. Instead, patients have complex medical issues leading to increased risk of thrombosis.

Interviewees also noted that it is difficult to conduct trials to demonstrate efficacy due to the rarity of thrombosis in pediatrics; a lack of communication among subspecialists resulting in anticoagulants being started prior to consultation with hematology; both physician and parental concern regarding frequent monitoring and blood loss; difficulty of obtaining consent for the enrollment of the vulnerable pediatric population; and concern for intracranial hemorrhage with anticoagulant treatment in the neonatal period.

Finally, interviewees noted that unlike in the pediatric oncology population, the culture of most patients going on study does not seem to exist

in the pediatric thrombosis population.

Given the list of challenges which exist in developing anticoagulants in the pediatric population, interviewees were then asked to describe what they saw as resources for facilitating successful anticoagulation trials in the pediatric population. Seventy-three percent of those interviewed felt funding would help to facilitate such trials. Fifty-five percent suggested the creation of a pediatric hematology trials consortium.

Other mechanisms for facilitating successful trials included decreasing the bureaucracy of getting trials open; enlisting dedicated staff, such as research coordinators and data managers; and providing technical preparation on behalf of investigators prior to opening the trial; for example, where labs could be sent out or what is to be drawn.

Furthermore, interviewees stressed the importance of a strong presence of a thrombosis investigator, both institutionally and nationally or internationally, to promote the trial and promote

accrual to the trial.

When asked what anticoagulant drugs most warrant investigation in the pediatric population, 8 of 22 interviewees stated that oral anticoagulants, including oral direct thrombin inhibitors, would warrant further investigation. Other studies felt to be warranted included studies of newer formulations, those drugs with established monitoring, drugs with reversibility, and trials which compare systemic thrombolytics to traditional anticoagulants in attempts to decrease the post-thrombotic syndrome.

Interviewees also noted that specific pediatric populations were in need of further investigation of anticoagulants. These include the neonatal and newborn population, the pediatric oncology population to help determine duration of anticoagulant or when to hold for thrombocytopenia, and, in addition, patients in need of long-term anticoagulation should be studied.

Also important to interviewees is the general consideration of answering basic questions in pediatric thrombosis, including how long to treat,

how intensely to treat, evaluations of prognostic subgroups, outcomes in patient subgroups, and standard and extended thrombophilia testing.

In addition, the development of a standardized clinical trial would provide for accumulation of data for standardized care instead of anecdotal care, which would be more informative. Finally future directions for anticoagulant development should include consideration for trials answering multiple questions.

Members of industry were also contacted to be part of a general discussion of anticoagulant drug development in the pediatric population. Twelve companies were identified with experience in developing anticoagulants and contacted by telephone or email. Of those, six responded with interest in discussing these issues with the agency.

We first inquired as to the company's experience conducting trials investigating nonmalignant pediatric hematology conditions, such as thrombosis, hemophilia, sickle cell disease, or immune thrombocytopenic purpura. Six companies had

experience conducting such trials. Four companies interviewed also had experience conducting trials which investigated anticoagulants in the pediatric population, while three companies stated they had successfully completing a trial investigating anticoagulants in the pediatric population. One company, who also had experience, was unable to complete the trial.

For those who conducted successful trials, trials which accrued their patient population and were completed, company representatives cited several factors involved to which they attribute that success, including using a targeted age group; having an available consortium of pediatric investigators; having a dedicated company team overseeing the trial; having a strong data safety monitoring board; having a key leader in the field of pediatric anticoagulation as the trial PI, who believed in the trial; and having an affiliation with a prestigious institution with excellent laboratories to conduct a single-institution trial.

We also inquired if companies had any

reservations regarding the off-label use of anticoagulant products in children. Five of six of those interviewed stated they did have reservations regarding such use. All companies were interested in broadening the labeling to include pediatric use of anticoagulant products.

When asked how a company decides on the number of institutions in which to open a study, answers varied from a dependence on the trial indication, endpoint, and effect size being measured, to more specific formulas for institutional recruitment. One company reported that they recognized that the best investigator estimates can never be definite, and therefore assume enrollment will be 30 percent of that predicted by the investigator, and recruitment to take one and a half to two times as long. A second company assumes 25 percent of the investigator-predicted accrual.

We also inquired as to why early development trials did not include pediatric patients. Members of industry interviewed were unified in the position that while there is a need for anticoagulant drug

development in pediatric patients, there is also a desire and a need to characterize the drug prior to moving it into the younger and more vulnerable populations of patients.

We also inquired as to the potential motivating factors to pursuing trials investigating anticoagulants in the pediatric population. Answers included the safe use of the product in children, unmet medical need, and pediatric exclusivity. Although the potential to be granted pediatric exclusivity was noted, companies also said that studies requested in the written request must be feasible to provide any incentive.

Like academicians, industry members acknowledged a number of challenges which exist in the development of anticoagulant products for the pediatric population. Five of those interviewed stated that indications for pediatric thrombosis are often too narrow to achieve the required accrual. This is not always realized at the initiation of a trial. Indications or eligibility criteria can be too narrow because they require patients to have, for

example, cancer and a thrombotic event, or a requirement to be treated in combination with another anticoagulant in addition to the study drug.

Three of those interviewed also cited that often there are too few participating institutions to reach necessary accrual. Two companies noted that other anticoagulants which may have simultaneously opened studies are now becoming a new issue in patient recruitment.

In addition, other challenges were also identified. Interviewees discussed the rarity of pediatric patients with thromboses and the medical complexity of the pediatric population at risk for thrombosis. Many patients eligible for a trial may already be on another treatment trial for their primary diagnosis, and therefore unable to participate in a second trial investigating an anticoagulant.

Dosing formulations usually do not exist for the treatment of patients less than 20 kilograms, and those interviewed stated it is often cost-prohibitive to have a participating institution who can only

enroll one to two patients.

Interviewees noted that the study design should offer an incentive for patients to participate, and that the trials must not only be feasible from a company perspective, but they need to be feasible from a parent's perspective as well. The multiple sites of intravenous access, needle sticks for pharmacokinetic and pharmacodynamic data, and frequent monitoring, which are necessary as part of such trial designs, offer little incentive for families to participate.

Interviewees also reported reasons for study site refusal to participate. These include lack of suitable patients, absence of potential benefit for the children, thromboprophylaxis in pediatric patients with central venous lines is not the standard of care, drug is not yet approved in adults, and site participation in another ongoing phase 1 anticoagulant trial. In addition, differences in requirements of the Food and Drug Administration and the European Medicines Agency were identified.

In conclusion, although these discussions

were limited in the numbers of those interviewed, attempts were made to facilitate discussion among important stakeholders in the drug development process for anticoagulants in pediatric patients. Members of academia and industry agree that the development of anticoagulants in the pediatric population is both needed and desired.

Clearly, there are pathways to conducting successful trials and investigating anticoagulants in the pediatric population. However, the challenges which currently exist need to be further explored through focused discussion, and methods to overcome these challenges need to be employed as we move forward.

Thank you.

Clarifying Questions from Subcommittee

DR. BALIS: Thank you, Dr. Snyder.

The floor is open to the panel for questions about this informative survey. Dr. Minniti?

DR. MINNITI: Yes. This is a very informative session. Thank you very much.

I just wanted to say that the challenges that

we are facing in pediatric anticoagulation agent are no different than the challenges that we face in other rare diseases. And this presentation reminded me of work that I am doing, looking at challenges in enrolling patients in the sickle cell population.

I have to second that many of the items identified were almost superimposable, and especially the funding or the number -- the need to have enough institutions contributing; the problem of the investigators buying in, into the trial, so uninterested investigators. But most importantly, I think, is the culture.

While in pediatric oncology, we have spent the last 30 years developing a culture that I think we all have ingrained, that there is no way. I'm not going to do anything possible to enroll a new leukemic on an available protocol. I don't think in the hematology world there is the culture that every subject -- every patient is a subject.

In the paper that I'm just submitting, we had a recent NHLBI trial that failed to achieve its target population. There were over a thousand

potential patients, potential subjects, that presented during the institution's -- during the enrollment trial time, and yet only 38 were enrolled.

So even though we don't have enough patients -- and I'm seconding what Dr. Reaman was saying. It's not just the patients. It's just difficult for a number of issues, and I don't want to, you know, tell all of them, the one that I found in the population that I'm more familiar with. But I'm saying even in adults, there are challenges to enrolling patients when there are limitations with a rare disease and the difficulty of convincing the investigators of the importance of enrolling every single possible patient.

DR. BALIS: Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Balis.

Interestingly, the same part of that presentation resonated with me also. And I look at it from an adult perspective. So when we're running trials at Cleveland Clinic, we have a couple of different mechanisms for running those trials. We have data support and nursing support that are paid

for through cooperative group funds, and that is basically a labor of love; we lose money on those, and we have some support that comes through industry funds. And data managers and research nurses bill their hours against those funds, just as a lawyer would bill against a client's funds.

So within pediatric hematology and oncology, does most of your support come from Children's Oncology Group funds, or does most of it come from industry, or is it the same mix? And is that the challenge to opening a study like this?

DR. YOUNG: Are you talking about the anticoagulation trials or --

DR. SEKERES: So I specifically said hematology and oncology, because I don't know how it works on your side of the fence. So on our side of the fence, it's a blend of those two models that I just mentioned.

DR. BALIS: Yes, Dr. Reaman?

DR. REAMAN: I can just give a little bit of a historical perspective because it actually goes back more than 30 years. It's probably more like

50 years. But there was a time when cooperative group support and the infrastructure that institutions could develop could support the oncology trials as well as support some other trials, hematology-specific trials.

Now there's insufficient support from the cooperative group mechanism to even support oncology trials. So trials, many oncology trials, aren't being opened at many institutions because of the shrinking level of support, and there certainly isn't any additional support for non-oncology trials.

So the only way that these can be successful is if there's either sufficient grant support or industry, sponsor support. And I think that's what's really lacking.

DR. SEKERES: So then getting back to the question I just asked, from the pediatric hematologists/oncologists on the panel, do you have enough industry trials open at a given time to support FTEs for industry trials or not? Or are they so spare that you do it only if you have enough subjects?

DR. BALIS: Well, let me address it, because I think the one other area that we get support from that may be a greater proportion in adult trials is philanthropy. So foundations and contributions support a lot of I think especially larger institutions' infrastructure. And that tends to be more stable support I mean, the problem with industry studies is the fact that we enroll few patients. It's difficult to do them efficiently.

So larger institutions that enroll a lot of patients on cooperative group studies and can consistently enroll on industry studies can potentially get enough infrastructure funding that way. But I think for smaller institutions, it's just -- you can't have a person for 10 percent time and then tell them to go find some money somewhere else the rest of the 90 percent.

DR. SEKERES: Well, that's right. The reality on the lines, when we do a trial, is we're always about three years in arrears with paying our staff's salary. Right? We have to pay out of pocket for three years until we close the study, get those

monies in, and then we kind of repay ourselves for the amount that they billed to those studies.

So if you don't have that concentration of industry studies in place, you can't do an industry-sponsored study for an indication like this. Right? So we're talking about not only a mandate for doing studies like this, but also a mandate for support for studies like this. Right?

DR. BALIS: Yes.

Dr. Shurin?

DR. SHURIN: Yes. I think this is an excellent presentation and certainly identified many of the big problems. Keep in mind, though, that we manage to get trials done on clotting products. Okay? And I think the big difference in terms of hemophilia as we're developing new clotting factors -- I mean, it's also rare diseases, but those tend to be primarily taken care of by the pediatric hematologists. There's already an infrastructure in place through the hemophilia treatment centers to enroll patients. They come to our attention. And there was a very strong motivation by industry to

develop these products because they were going to make, and have made, a lot of money.

Industry isn't motivated the same way. We don't have the same organization. Many of these patients are in the intensive care unit, in the pediatric intensive care unit. They're taken care of by other people. And so the hematologists are, at best, consultants; and often, and I think this came out in the responses to this survey, not even called until fairly late in the game. And, therefore, you don't have people that can actually enroll.

I think one of the things to look at is to perhaps be a little bit creative about using some of the existing infrastructure. And I would really urge that we think about doing that. Definitely more money is needed, but the idea that there's going to be a parallel infrastructure to support anticoagulant studies in children is a complete fantasy.

So you have academic pediatrics, which is in economic difficulty. You have nonmalignant hematology, which is dying on the vine. And the combination of this is we really need to provide both

the infrastructure and some more resources to actually do this.

There are places where some of this infrastructure is in place, and I would say that one of the things that might be worth considering would be exploiting some of the existing infrastructure. For instance, Children's Oncology Group is set up to do oncology trials. Could it be resourced so that you get clotting disorders in cancer, which are, of course, quite common? We all see them. Are there ways to infuse funds into that existing infrastructure which already has the data management and various other kinds of things, and also has the patients?

There are perinatal and neonatal networks that are run through the NICHD. These would be an ideal place to do studies in newborns. There are the CTSA consortia, which are now set up across the country, have a pediatric subgroup within them. They're looking for trials.

I think when you look at setting up any kind of infrastructure which is going to be ongoing, you

want to have a sense that you have the depth of potential studies to justify this. This is the reason that the cooperative groups have been so successful, a leukemia study closes, another leukemia study opens. You have a whole bunch of studies going on simultaneously. And unless you can give sort of the scientific justification for what are the studies that you're going to do so you're not setting up infrastructure to conduct one study which will have 60 patients, that isn't going to happen, and I think being realistic in terms of what's needed, and what's really needed, because the honest truth is that much of the support, some of it comes from philanthropy.

Not a small amount of the support for the research that goes on in pediatric hematology/oncology comes from the patient care income of the physicians, who pay those nurses and pay for that kind of infrastructure. And I think the key issue is to try to do something which is more sustainable than that because that's obviously not been sustainable.

DR. BALIS: Dr. Young, do you have a

question?

DR. YOUNG: Yes. I could just add just from my personal experience. Even though I'm a pediatric hematologist/oncologist, I really only do hematology now, and so I'm not involved in COG trials, and neither is my staff. So how have I accomplished some of what I've been able to do by having a research team is really economies of scale and, as Dr. Shurin just said, running multiple studies in hemophilia and thrombosis, some of which are industry funded, some of which are federally funded.

I mean, the money comes from all kinds of different sources and then sort of gets pooled. And by having this constant stream of studies going, that's the way that I can justify keeping a team intact. But I'll tell you that it's not easy to do that, because as soon as one study is coming to a conclusion, the next thing, I'm like, okay. Well, how am I going to fill that funding bucket? It's kind of like keeping a pail full of water that's got a constant leak to it.

DR. BALIS: Dr. Luban?

DR. LUBAN: I would just add that if you look at most pediatric hematology programs that may or may not be incorporated into hematology/oncology programs, for the most part, the hematologists do both bleeding and clotting. So there's a natural synergy in combining those two together and gives an academic focus to most hematologists.

The other point that I would make is that everybody's budget is shrinking, and the hemophilia treatment center budgets, which are currently funded by mostly CDC and MCHB, are also shrinking. So to put more clinical trials in that stream could become problematic in the future.

DR. BALIS: Dr. Kaskel?

DR. KASKEL: Two weeks ago, Friday, we had a meeting at Natcher on the CTSA. The child health oversight committee of the CTSA had a meeting on quality data, acquisition of quality data in clinical trials in pediatrics. And much of what was very nicely presented here for the challenges was mentioned there.

What I remember were some of the concepts

that we could take from that and apply here involving harmonization of data and harmonization of existing networks, the importance of the network. So if you're looking at a multi-specialty approach to this problem, not just oncology/hematology, then you have to take advantage of identification of the currently existing networks and harmonize them together within the infrastructure. This is really taking advantage of lots of work and funding that went into setting up these networks.

Also, the other interesting advance that has come from some of the work of the CTSA is the common IRB, and now the National Children's Study has a common IRB. And Steve Hirshfeld has heralded that approach, and that's going to obviate much of these barriers to getting multi sites up and running. You're either with a common IRB, where your institution buys in, or they're not part of it. So this will facilitate contracts, and the IRB process will be under one umbrella. And this was what Steve has felt for a long time, that the National Children's Study had to be done.

So there are two rays of hope on the horizon where we could take some of that and apply it to this.

DR. BALIS: Dr. Shurin?

DR. SHURIN: The CTSAs are also working on a central IRB. And, of course, the advanced notice of proposed rulemaking revision has a central IRB for multicenter sites.

Just a comment on Dr. Luban's comment. My proposal would not be that the hemostasis and the hemophilia centers take on something else without reimbursement. I think the potential for infusing new funds into that existing mechanism might be beneficial on both ends.

So I think the key issue is how do you make it so that you're not creating multiple unsustainable -- because they're too expensive and too heavy and too cumbersome -- sets of infrastructure, but use the existing infrastructure where it's possible? There's quite a lot of it.

I think the key issue is to start by enunciating what are the questions you want to solve

and then what are the mechanisms for doing it, rather than starting with the mechanisms and then trying to think, well, what problem can you solve using that mechanism? I think we need to be much more strategic about it and really start with a focus on the science. And the fact that we have some potentially very exciting new agents coming in with different mechanisms of action ought to be a motivator for that.

DR. BALIS: I think one of the advantages, at least we can see, in oncology in cooperative groups is there's somebody -- when the group exists, there's some mechanism for prioritizing, which is, I think, critical for doing studies in kids as finding -- outside of a multitude of industry partners who all want their products developed, somebody needs to look at that scientifically and make a decision.

Dr. Snyder, can I ask you one very brief question, and then maybe have you propose or think about what you've learned from your study and how you might think it moved forward.

The question is that you had mentioned that there are a number of institutions that had their own guidelines or clinical protocols for using these agents. Did you attempt to collect those? Do you think they'd be useful in terms of looking to see how people have worked it out individually through clinical experience?

DR. SNYDER: I think it would absolutely be useful. But, no, I didn't attempt to collect them. I think that much of what we have available, we can all access. Those institutional protocols are likely from chest guidelines that are modified, published papers, anecdotal experiences. And I think, as hematologists, pediatric oncologists/hematologists, we probably all have access to those same things.

But it's a matter of somebody sitting down and making it a priority, and seeing that it's a problem in that institution, and saying we need to have this done. It needs to be done this way for every patient. These are the labs we need to collect. This is the blood we need to draw. This is when we should do it. This is where it's going to be

sent. This is what we're going to do for the NICU babies. This is what we're going to do for the older children. And somebody needs to take the time out of their day to do that, and I think that that probably doesn't happen at all institutions.

DR. BALIS: There are mechanisms through consensus conferences, I think, to do that more on a national basis, and that may be some way to pull this together.

Do you think, based on what you heard back from industry and academia, that it's feasible to do these studies going forward that we're here to discuss?

DR. SNYDER: I think that everybody agrees that right now, feasibility is one if not the major issue. But I think that having this meeting today is going to open a dialogue that didn't previously exist or existed maybe in a small group of people, and we're trying to encompass a larger group of people now. And so I'm hopeful that the great minds will get together and make plans for a path forward.

DR. BALIS: Thank you.

Dr. Freedman? And I think after Dr. Freedman's question, we'll move on to Dr. Young's presentation.

DR. FREEDMAN: It does seem like this issue for pediatrics is different from the general oncology products. And if you put aside the important issues of financing these studies, and the infrastructure is terribly important, but having a gap in the labeling for a drug that's used commonly to treat patients or to prevent issues is a serious public health issue. And I think we need to acknowledge it as that.

My question, really, is to the FDA, is acknowledging the fact there's a potential conflict which you may have in assisting product development, are there resources that can be made available by the FDA for this type of issue to encourage the conduct of the studies?

I know you mentioned the patents issue, the six-month extension and so forth. But apart from that, are there other things that the FDA can do to facilitate the conduct of these studies, maybe in conjunction with NCI?

DR. FARRELL: We are internally deliberating on options and possibilities, but we actually wanted to hear from the committee here. I mean, I think some of the questions that we have at the end of the session are designed to get your feedback on what we might be able to do, and also thinking globally what we should do with, perhaps, our European partners in order to get this done.

DR. BALIS: Thank you. We're running a little bit behind, but I think this has been a good discussion to have and probably touches on some of the questions we're going to talk about later. Thank you, Dr. Snyder.

So we'll move on to Dr. Young's presentation.

Speaker Presentation – Guy Young

DR. YOUNG: Thanks very much. I really appreciate the opportunity to be here. I've dedicated much of my career, actually, to this area, and I think that the discussion I'm going to have now is a really good follow-on from what Dr. Snyder just discussed. So she brought into the discussion a discussion of the theoretical opinions out there, and

I will now take it to a little bit of the real-world setting of what's happened in actual clinical trials and what the challenges have been.

So I'll start with a little bit of background and go through that briefly, because some of that's already been discussed, and then get to my personal experience in conducting these clinical trials and let you know how they've gone; and then, at the end, discuss my perspectives on what the challenges are.

So we've already discussed Dr. Raffini's paper. I will skip the epidemiology part because we've already discussed that it's increasing and what the issues there are. But I want to focus on this part that wasn't discussed, and I will come back to this again at the very end, which is the frequency of anticoagulant use.

So this is directly from Dr. Raffini's paper. And what you can see is the solid bar at the time top is enoxaparin, and the dashed line is warfarin. And this is probably the complete opposite -- in fact, maybe even beyond that -- of what you see in adults. In adults, warfarin is the mainstay. But in

pediatrics, regardless of your age, enoxaparin is the mainstay.

So in neonates, it's a tenfold difference between the frequency of use of enoxaparin. But even as you get to the older kids who do use warfarin more, there's still a fourfold difference between how many patients are on enoxaparin versus how many are on warfarin. And we do use enoxaparin primarily as the drug to treat kids with VTE. It's not that everybody stays on enoxaparin for the whole course, but, as you can see, certainly the majority do. So I'll come back to the enoxaparin issue at the end, as I think it's a bit of a cautionary tale.

So the current anticoagulants that are FDA-approved for children we've discussed. They're all right here in this box. And I have this discussion often when I give talks. And then we briefly discuss that there is some -- this is not to mean that this is FDA-approved, but the discussion about some guidance with respect to argatroban. And that's the only anticoagulant that has guidance. But it is not approved, and I need to point that out. I

probably should have changed the title as I animated this slide from here to here.

We've already gone through these, so I'm just going to skip this slide. I do want to mention that we're talking about anticoagulants, so we're leaving tPA out of this discussion, but that is also a drug that's used to treat kids with VTE. So basically, all of them are being used, as has been discussed.

So this is an interesting slide. I developed this for a talk I gave at ASH a couple of years ago, and went through the history of anticoagulation. So you see the columns here, the discovery of the agent, more or less; the time; the first clinical use. So this is the first paper that I found that actually used the drug. And then the first use in children; and then the first perspective study in children, actually, is the last column.

What you'll notice, actually, which is interesting, and I think there's good news/bad news, the bad news side of it is that the time from first clinical use in adults to the first clinical use in children -- I'm talking about clinical use, a case

report, not a clinical trial -- is shrinking. So, in other words, pediatricians are getting more bold and saying, well, it's been approved in adults, and so I'm just going to go ahead and prescribe it to a child.

The somewhat more encouraging side is -- and, granted, these prospective studies are small, and we've discussed that these are not like adult prospective clinical trials with thousands of patients, but the time between the first clinical use in children and first prospective study in adults, that's also shrunk somewhat as well. So we are getting more interested and devoted to doing these studies more quickly from the time of first clinical use to first prospective study.

Now, the new oral anticoagulants, I'm not aware of any reports so far, although I was interested to see in the survey that, actually, somebody -- or two people, I think have said they've already used one of the new oral anticoagulants in children. So that's why I have this line, which is, it's just a matter of time. I mean, somebody out

there is going to put a 12-year-old or a 14-year-old on dabigatran or on rivaroxaban, and it's just a matter of time before the report that as a case report.

So for the duration of my talk, I'm going to go through the trials that I've been involved in and that I've conducted. And I put a timeline on the bottom just to give you some sense of how long these trials take. And it's almost comical how long they take relative to how many patients are in the trial. If I did a formula of number of patients divided by years, those numbers would all be in the single digits. Right? So 15 patients, 7 years. Right.

So this is the sequence, and the point in here with the arrow is just that this is a timeline. So I've done one study with bivalirudin. You can see the timeline there. That was published in 2007. Argatroban. At the last slide, I'll have the references. Fondaparinux was just published literally about a month ago. Bivalirudin, notice this is coming off the page. That's on purpose because that's not completed yet. That's undergoing

data analysis. And I'll describe each of these studies in a little bit of detail, including the challenges.

Then this one you can't read. This is rivaroxaban. There; you can read it. So this one is a trial that I'm involved in. And I did not mention here apixaban or dabigatran, but I'm aware of trials that are ongoing with those drugs as well.

As I go through this, I will mention the names of drug companies. It's just to illustrate certain examples. It's not to pick on any of the companies, per se. So if any representatives of those companies are here, don't throw any darts at me, please.

So the first bivalirudin study was an investigator-initiated study that I conducted. And The Medicines Company is the company that makes bivalirudin, and the study was conducted under the company IND. Protocol development started in 2001, only included patients less than 6 months of age because these were the ones that didn't have as much antithrombin, as you heard before. So we thought,

hey, it makes sense. Let's use a direct thrombin inhibitor in this patient population. They're the ones that are deficient physiologically in antithrombin.

In two sites, we enrolled 16 patients over three years. And granted, again, these are patients less than 6 months of age, and the study was published in 2007. Again, I have a slide at the end that has the references.

So what were the challenges? So enrollment was really slow. Limited funding from the sponsor. Only two participating sites. And the families were really quite reluctant to enroll their child on a study. These are newborns, generally speaking, vulnerable. They have other medical problems. And some of them, as soon as I said, hi, I'm Dr. Young; I'd like to talk to you about a research study, that was the end of the conversation. They said, thank you very much, but we're not interested. I said, I didn't even tell you what it's about.

Pharmacokinetics this time wasn't done; pharmacodynamics in the sense of measuring a PTT

only. So there isn't really what's truly pharmacokinetics. And then there was really no support for a follow-up study. So I approached the company to do a follow-up study, and they said, no, we're not going to do that. You'll have to find other funding.

What were the positives? So it was the first actually completed study of an anticoagulant in kids since the trials completed for enoxaparin in 1996. So there was a 10-year gap between any kind of prospective study in pediatric anticoagulation.

The Medicines Company was the only company at the time that was willing to support me to do that study. And if you're wondering how I got to this, I literally cold-called -- maybe the industry people would appreciate this. I cold-called industry, finding their research division, and just tried to find the right person on the phone, and tell them who I am and what I'm interested in. And the Medicines Company said, oh, okay. Let's talk about it. And so I do appreciate from that company that they did support me to do that study. Two other

companies -- I won't mention who they are -- were not interested.

As a result, I actually built a very good collaborative relationship. We're talking about academia and industry working together. We built a good collaborative relationship. They then did a study for their -- I think it was their PREA requirement, or their BPC; I think it was PREA, but to do a study in cardiac catheterization in children, which is the adult indication for this drug. And I served as a support and consultant for that study and helped them with study design elements, and actually ended up as a co-author as well, an unpaid consultant for the study.

Okay. Argatroban, a little bit of a different story. So this was an industry-initiated and sponsored study under the company IND. Now, I'm not exactly sure when the protocol development started because I wasn't involved. I'm guessing it was somewhere around 1999. And this was for patients with confirmed -- and I stress confirmed -- heparin-induced thrombocytopenia, which is quite unusual in

children.

In 2000 to 2003 -- I actually got involved in the study some time in 2002 -- the enrollment was zero. So they spent four years, and they enrolled no patients. And in 2003, I was actually approached by the company to serve as the PI to try to revitalize the study, along with an adult hematologist, Lynn Boshkov from Oregon.

So we met and we significantly revised the study. We added other centers. And then the study resumed, or really started over in 2004. And over 18 years -- it feels like 18 years -- we accrued 18 patients over 3 years. And there have been two papers published from this, including a clinical manuscript -- which says PK, but it's really PD manuscript -- that was done collaboratively with the FDA, and I'll get back to that in a bit.

What were the challenges? I think originally the company -- I don't think they knew who the experts were in the field. And when I met with them, I said, well, who's kind of leading this effort? I didn't, frankly, even know who the people were. They

weren't hematologists, I'll say that much, and they weren't really experts, not that there is necessarily an expert in pediatric HIT, it's so rare. But these were not people who are experts even in adult HIT.

The study was designed really poorly. In fact, if you looked at the inclusion and exclusion criteria, basically all of the exclusion criteria essentially nullified all the inclusion criteria. It was almost like you could not even enroll a patient on the study. So not surprisingly, they didn't enroll any.

They also, I don't think, chose participating centers particularly well. They didn't choose centers that were large children's hospitals that may see patients with this. So I think there was just a lack of knowledge on behalf of the drug company, through no fault of their own. I don't think that -- I mean, I'm raising that as an example of where we may be able to work better together. And so three years of work was done for no subjects. Then, after the study was redesigned, there was completion of the study. But, ultimately, there was a really

long delay in completing the study from the inception, which was, I believe, again in 1999.

Then there was a really nice collaboration with FDA in terms of doing some very interesting pharmacometrics, which were published separately. And that was great, and it was very fruitful. But that whole collaboration, with negotiations and discussions, that led to a two-year delay in actually publishing the study. I mean, the data was done in 2005; the study wasn't published until 2011, or I should say 2007 to 2011. So it was a good collaboration, but there was a delay there.

The positives is that GSK then formed a new steering committee and followed the recommendations made by the steering committee, which led to successful study completion. And I think the collaboration with FDA led to a really robust PK analysis, which was really a PD analysis, despite a sparse number of samples from a small number of subjects. But some interesting pharmacometric techniques, which it took me a while to even just begin to figure out with pharmacologists, clinical

pharmacologists. It really was excellent and, in fact, led to a separate publication, of which the FDA is the primary, the lead author.

Then this is still the first and only anticoagulant -- I'm not sure if the word "pediatric labeling" is correct; you guys can correct me -- with some language that discusses pediatric dosing.

So fondaparinux, so this was an investigator-initiated study under an investigator IND. So I got an IND to do this study. And this study -- we talked about what can FDA do to support studies. Well, FDA actually has a mechanism that can support these sorts of studies from Orphan Products Drug Division.

So I found out about this granting mechanism, and I said, okay, well, I'll apply and see what happens. And, fortunately, I did get funded to do this trial, again from Orphan Product Drugs Division under my IND, not the company IND.

So this was for children with DVT, but only older than one year. That was an IND restriction. After going back and forth a few times, the FDA felt it was not -- they were uncomfortable. It wasn't

safe to really explore studies in children less than a year.

So we enrolled patients between 2007 and 2009. We planned to enroll 24 subjects. I agree, it's not a lot, but that's what we planned to enroll, and we in fact enrolled, and we fully enrolled. And the study was just published in paper last month. It was published online some months ago.

The challenges. So here's a very interesting story. This is like a two-year story that I'm going to just make really brief. So I originally actually approached industry, just like I did with The Medicines Company, to do a study on fondaparinux in kids. It was first Sanofi, and then Sanofi sold the license of the drug to GSK. And I'd already had a relationship with GSK because of argatroban, so I thought, okay, great. This should work out. And they said that they weren't interested, and they were going to apply for a waiver of PREA to conduct a pediatric study, which, as you may understand, was not granted.

So I got the grant from FDA after that, and I

started the study. And then a couple years later, they approached me and said okay, we didn't get the waiver so, "Dr. Young, let's talk about doing the study." And I said, "Well, I don't really need your help any more." They said, "No. We want to work with you." And I said, "Well, honestly, the study's fully funded, so thanks but no thanks."

Then a lot of time passed, a lot of conversations between GSK and FDA and GSK and me. And, ultimately, once we published the data, it was licensed -- the study data was licensed to GSK under an agreement, a data transfer agreement, between my institution, basically, and GSK. So it's kind of an interesting story.

When I first went to my technology transfer, the intellectual property office, and I explained to them that a drug company wants to license or have this data transferred. And they said, "Isn't this the company's drug?" I said, "Yeah, yeah, it is." They said, "Well, why do they want this data from you? Don't they have that data?" And she couldn't even understand -- it's sort of like the reverse

relationship. Right? The company's buying data on their own drug. But eventually we were able to get to an agreement, and so they've got license to the data.

Now, the study didn't include children less than a year -- that was another issue due to the IND restriction -- and there was a short follow-up period of just basically a month, really. It was, again, a PK and short-term safety study, or PD.

So the positives. Well, FDA funded the study. So there are ways to get funding from FDA. There are mechanisms to do these sorts of studies. The study actually completed relatively, I'd say, quickly, with four participating sites, which is not that many. And then with this relationship that I've developed with GSK, we're now collaborating to obtain follow-up data.

I was planning on obtaining all this follow-up data; it turns out GSK needs the data. So rather than not working together like we did the first time, we decided, okay, let's work collaboratively together. And then I'm also working

to help GSK, again, as an unpaid consultant, to support their efforts to meet their FDA postmarketing obligations.

The last one I'm going to go through -- well, actually, I have two more to go through, but they'll be fairly brief -- the second bivalirudin study . So, remember, the first bivalirudin study was children less than six months, and the company wasn't interested in studying the drug any further in children with VTE, anyway; they did do a cardiac catheterization study.

So I wanted to, obviously, close the loop here, so I applied for a grant to NIH and was fortunately successful enough to get that grant. By the way, if you think that every grant I apply for, I get, I can assure you that is not the case, not even close. But this one I did image to score high enough to get the funding. And we studied DVT in children that were not originally included in the study, so greater than 6 months to 18 years. Notice the 18 years. And the study accrued, however, only 18 of the 30 planned patients. Data analysis has just

begun.

So challenges. Funding was somewhat limited. This was an RFA mechanism. There was a good amount of money, but it was hard to do a lot of the planning aspects in the development of the study. And I appreciate that NHLBI now has a new mechanism to help with planning grants for these sorts of things, which I think is very wise.

Then, interestingly, several sites didn't accrue any subjects in three years, which was rather surprising. But the slow recruitment overall was due to the fact that this is a continuous infusion drug. There was a PK requirement; this time when I say PK, I mean PK. We did bivalirudin levels as well as PTTs. So it was a challenging, challenging study to complete.

When I told my research staff that we were going to just stop at this point and not go for another one-year extension to continue the study, the smiles on their faces were really -- I should have taken a picture. But it's been a challenging, very challenging, study to do.

The positive is NIH funded the study, so there's another way of getting some funding to do these studies, is through NIH, though I will tell you that it's not easy to get that sort of funding. The study generated over 200 matched PK/bivalirudin levels and PD, so we should have a nice, robust analysis looking at both PK and PD. And this is a first for a pediatric study. The other studies all just looked at pharmacodynamic parameters. And so we'll see what the limitations of the PTT -- which we all, I think, realize what they are. This study may really bear that out very nicely.

The Medicines Company, I've had a good relationship with them. They provided study drug, so that reduced the cost to the federal government from the grant. And then I also got a sense of some sites that really recruited patients really well. We talk about, in some of the challenges, having sites that are willing to recruit, that have the infrastructure. Some sites recruited amazingly well for the study. Others, even from large children's hospitals, recruited none in three years, which was shocking and

disappointing.

Lastly -- this will be brief -- rivaroxaban is industry-initiated and funded by Bayer. The first phase of a three-phase development is underway, and the goal is to complete all three phases by 2017. So far, there's been, again, slow recruitment, a recurring theme. This is a very select population, and it's been difficult to recruit, although it is moving along. It's not really that far behind.

The positives here -- and this is, I think, a good lesson -- is that Bayer very early on formed an advisory board of international experts. They actually went to coagulation-specific meetings, the International Society of Thrombosis and Hemostasis, and sought out experts.

So I gave a talk at that meeting on where we were with new anticoagulants. This is in 2007. And one of their representatives came up and spoke to me afterwards and asked me if I was interested in participating because they were starting to look at this.

So I think that was wise. They started early

on in the process. They identified the real experts in the field to form an advisory board that, over two years, helped them to generate a plan for pediatric development. And that's because, of course, EMA, as you're aware, has its own requirements for developing a pediatric investigation plan.

I don't want to -- if there's representatives here from the other companies, which I think there are, for apixaban and dabigatran, there are trials in pediatric development as well. I don't want to exclude them. I know that those are happening. I personally am not involved in them, so I can't give any details about that.

So from all that, what have I learned in the last 10, 11 years? So what are the requirements for success? Funding. We've heard that before. I think Mother Teresa -- and I'm quoting Tom Abshire, a hemophilia expert, who uses this quote a lot, says, "With no funding, there's no mission." So you can have whatever mission you want. We want to do these trials; we want to do this. If you don't have money, it's not going to happen.

So although I was successful in obtaining federal funding for two studies, it's not easy and it's extremely time-consuming. I mean, writing those grants -- those of you who have written grants in this room know what a time-consuming process that is, and yet you don't even know if you're going to get funded. I mean, the funding line is 10, 20 percent. I think on that RFA that I got for bivalirudin, there were 32 grants, of which 8 were funded, so 25 percent, which is actually not all that bad. But still, 75 percent of those grants never got funded.

Now, with new regulations, particularly the EMA regulations, funding for new drugs like the ones, the rivaroxaban, dabigatran, apixaban, that funding is now available. However, I would say that funding should not come only from industry because industry's agenda may not be in line completely with academic pursuits.

Now, we do work together. We want to do some additional studies as we're doing these studies, not just to fulfill a requirement. And so working collaboratively is important. But I don't think

funding should solely be from industry. That's my personal opinion.

Collaboration between academia and industry, that's a requirement for success as well. Industry sponsors need to know who the experts are. We talked about argatroban, what a delay there was because, in my view, the wrong experts were selected; versus rivaroxaban, where things are proceeding more expeditiously and I think in a better way.

Industry sponsors, I think as I mentioned, should form advisory boards or steering committees early in the process. And then academics and clinicians, whether they're on the advisory board or steering committee or not, really need to work to open and recruit patients on studies, and I think you've heard that from the previous presentation as well.

Then collaboration with regulatory authorities by both academia and industry. And so I'm going to give you the good example and the bad example. They both happen to be related to GlaxoSmithKline, so we have the good and the bad for

both of them. And, again, I'm not picking on GlaxoSmithKline per se.

So for fondaparinux, the FDA restricted my investigator-initiated IND to children greater than one year. They said, nope, you can't do that. I said, okay, fine. And now, when GSK went back to the FDA to fulfill their obligation, they said, "Well, how come you don't have data for children less than one year?" I mean, that literally happened.

So they actually asked for my IND letter. I provided that to them so they can see that it just wasn't -- the FDA restricted it. So we don't really have good collaboration between academia, industry, and regulatory.

But a good example is the argatroban example, where we worked with FDA collaboratively, GSK and FDA and myself, to do this data analysis. And as a result, there's a nice PK manuscript with authorship from FDA, from GSK, and from myself. And I think that's a great example of how we can work collaboratively together. So we've got the good and the bad.

What should not happen? This is my cautionary tale. So that's the enoxaparin example. And, again, I'm not trying to pick on the drug company that makes enoxaparin, although it's generic now as well.

So this is the most commonly prescribed anticoagulant in children. I would even say, based on the Raffini, it's really by far the most commonly prescribed. Yet there's no industry funding for ongoing research. There's no FDA approval, and I think there's any planning for any approval or labeling. And, again, this is the most commonly prescribed anticoagulant in kids.

There is no prospective data on safety or efficacy since about 1996. And yet there are concerns -- they were already brought up by the previous speaker, or previous speakers, I should say, Dr. Donoghue as well, about long-term use. Right? We use these drugs for months on end. I've seen patients who have been in enoxaparin for three years, and I don't know what it's doing to their bones.

I will say that I have seen actually a couple

of cases now of pathologic fractures in neonates that, you know, who knows? I mean, there are so many reasons why they might get a pathologic fracture. But these are neonates on enoxaparin. I can't imagine the enoxaparin didn't have some contributory factor. Again, it's a guess and an opinion.

So there's also still a lack of data on efficacy and bleeding as well. So now enoxaparin's gone generic, I don't know what can happen with this drug. But we really need even more studies on this drug alone. It's just being used rampantly, and we really have no data.

So I do put my money where my month is. With this new NIH mechanism, I have applied to do a study to look at enoxaparin versus fondaparinux, which supposedly doesn't affect bone, to look at the osteopenia issue. But, again, what are the odds of getting funded? Just because I got funded twice before doesn't mean I'll get funded this time.

So at times it's been -- I'll close with some pictures. It's been a lonely course. I've really been the one to push forward with these studies.

There are no other prospective studies. It's not that I just mentioned my own studies and ignored others; these are the prospective studies on fondaparinux, argatroban, and bivalirudin that are published. So these are the only ones, and it's sometimes been feeling kind of lonely. And it's for sure been an uphill battle, I will say very much an uphill battle. But working hard, you can get to the top and achieve something at the end of the day.

So, in closing, these are just the references, which I've listed as just the PDF titles. You can see the second one from the top has authorship. Dr. Madabushi is an FDA pharmacologist. There's some other FDA personnel on there as well as GSK and myself. And then the other studies, you can see some of the other contributors as well.

So thank you again for allowing me to participate in this meeting. I hope that I've been able to give you some insights there, and I'm happy to take any questions. But I think I'll just come and sit down and take them since we're talking at a roundtable.

DR. BALIS: Yes. Thank you, Dr. Young.

I think, in trying to get back on schedule, maybe one or two burning questions. Remember, we have an open discussion at the end, so we can get back to some of these topics.

Dr. Aly, I think you've joined us since we introduced. Could you just introduce yourself for the record?

DR. ALY: Hany Aly, professor of pediatrics, director of neonatology at George Washington University Hospital in D.C.

DR. BALIS: Thank you.

Well, if no questions, we have a break coming up, but why don't we hear from Dr. Artman, and then maybe we can take a break and get back if there are other questions afterwards.

Speaker Presentation – Michael Artman

DR. ARTMAN: Thank you. I'm honored and delighted to be here to talk about some of the issues related to thromboembolism in the congenital heart disease and cardiac surgery population. This is a subgroup of patients, I think, that also is a bit

unique and has its own challenges, and with a fairly high incidence and prevalence of thromboembolism.

So just for those of you who are not pediatric cardiologists, congenital cardiac defects continue to be quite prevalent in our society. Congenital heart disease is the single most common form of birth defect. And nearly 1 percent of every live birth in the U.S. is associated with some form of cardiac disease or cardiac defect.

Right now in the U.S., based on current estimates, there's about 800,000 children and over a million adults with congenital heart disease who are living in the U.S. right now. And due to advances in surgical and medical care, the survival rate is increasing.

That gets back to one of the earlier comments about the increasing incidence of thromboembolism in the pediatric population. And part of it, at least, in the congenital heart disease sector, is because these kids are surviving now and 20, 30 years ago they weren't. The adult population with congenital heart disease is projected to grow about 5 percent

annually. So it's a significant burden.

In the past, there hasn't been a lot of attention focused on thromboembolism in congenital heart disease and cardiac surgery, and it was considered to be a rare event. And all pediatric cardiologists and cardiac surgeons would say, oh, yes, we see this and it happens. But it's only been recently that it's been studied more carefully. And I'm going to focus my presentation on two or three papers that have been published in the last few weeks or months.

This paper that I'm referring to here came out of Hospital for Sick Children in Toronto, so a single site. And over three years, they reviewed over 1500 surgical cases and found a prevalence of 11 percent of embolism, thromboembolism, in those pediatric patients. And of those, 3 percent had multiple clots.

There were a multitude of complications. They looked at a number of risk factors, and found that younger age, less then 1 month, being on ECMO, extracorporeal membrane oxygenation, was a risk

factor; having a heart transplant. Cyanotic congenital heart disease and a history of previous thrombosis were all pretty significant risk factors for thromboembolism.

It appears that these patients are at risk for venous and arterial thrombosis for a number of reasons. They may have shunts that are constructed surgically. There's disruption of blood flow during surgery. The blood volume is exposed to a large synthetic surface as it goes through the pump during extracorporeal membrane oxygenation and during cardiopulmonary bypass. You all know better than I do what happens to your coagulation system when you expose blood to synthetic material. There's also a systemic inflammatory response that is generated. So there are multiple reasons and multiple factors that these children may be at risk for thrombosis.

It was clear from this paper that if you had a clot, it was a bad thing. I've highlighted in the boxes a couple of the major adverse outcomes: cardiac arrest, and the odds ratio, clot versus no clot, which was 4.9. In-hospital mortality, the odds

ratio was 5.1. So, clearly, these kids that develop thrombosis have worse outcomes.

It's difficult to tease that out. Is it really the clot? Is it because they're just sicker overall? These were the more complicated kids. These were the ones that had more challenging postop courses, et cetera. So it's difficult to determine cause and effect, but, clearly, these patients with thrombosis have worse outcomes.

So in addition to the cardiac surgical patients, who else in the pediatric cardiology arena is at risk for thrombosis? So in addition to those cardiac defects that I mentioned undergoing cardiac surgery, those patients who have prosthetic valves that are put in surgically; systemic to pulmonary artery shunts, so a Blalock-Taussig shunt, for example; and then those patients who have abnormal flow patterns, and an example is the Fontan patients, and I'll go through a little bit more of that in a moment.

There's also a segment of the pediatric population with heart disease who have acquired heart

disease. And the two main categories are those who develop giant coronary artery aneurysms following Kawasaki disease; those are defined as coronary artery aneurysms greater than 8 millimeters. And those are especially prone to thrombosis. And those patients are suspect for developing myocardial infarction acutely. And then also patients with severe dilated cardiomyopathy; they may develop thrombosis in the left ventricle or right ventricle or in the atria.

So the Fontan procedure, this is a very commonly applied surgical procedure now in our field. It was first performed in 1968, and since the original description, there's been several modifications. It's generally a staged approach. Infants will often undergo a couple of operations before they have completion of the Fontan circulation somewhere around 2 to 3 to 4 years of age.

Regardless of the technical approach, and there are several different types, but the net result is that systemic venous flow is directed into the pulmonary bed without the assistance of a pump, of

the ventricle. So you get very sluggish blood flow. So these patients are really at high risk for thrombosis. And it's used for a number of congenital defects, hypoplastic left heart syndrome being one of the more common. And, again, that's a patient population that 30 years ago didn't survive.

So in Fontan patients, thrombosis accounts for significant morbidity and mortality. We know that once a patient with a Fontan circuit has a clot, the mortality seems to go up, similar to what I just showed you about the acute post-surgical patients. It's up to 25 percent in some series in pediatrics, and even 38 percent in adults.

The rate of thromboembolism in Fontan patients, if you survey overall and look at the prevalence, it's variably reported, but anywhere from 3 to 33 percent. Part of this, I think, reflects our lack of a rigorous systemic approach to monitoring for thrombosis in these patients. It appears that about half occur early in the course, within the first few weeks or month. And, again, as I mentioned, I think we probably really underestimate

the true rate of thrombosis in these patients. We do know that if you don't anticoagulate or provide antiplatelet therapy in these patients, there's a substantial risk for thromboembolic death. And the hazard ratio is at least 90, if not higher.

So, again, there haven't been a lot of studies to look at anticoagulation in this patient population. This is a study that was reported very recently in the Journal of American College of Cardiology that was a multi-site study. It was conducted in several Canadian centers and Australia and New Zealand. Randomized 111 patients total, which was about half of their target, to either aspirin or warfarin. The warfarin was started after a heparin lead-in.

They followed the patients for two years and found that there was really no significant difference between these two therapies, and the thrombosis rate was really suboptimal for both treatments, as you can see, 21 percent in the aspirin group and 24 percent in the warfarin group.

One patient had a major bleeding event in the

warfarin group. That was associated with an INR of 11.9 when the child presented; again, illustrating some of the dosing issues, difficulties, with warfarin. Thirty-three percent on warfarin had at least one minor bleeding episode versus 14 percent on aspirin.

What I think we learned from this trial is that many of these thromboemboli were clinically silent. The monitoring included two transesophageal echocardiograms, one at three months and one at 24 months, at the completion of the study. Only 48 percent of the subjects participated in both transesophageal echos.

So monitoring by TEE in children is particularly difficult. Younger children need anesthesia, or at least very heavy sedation, so that's a problem. So detecting these thrombi inside the chest especially can be challenging and difficult.

The use of warfarin, you all know better than I, is very challenging in children. It was interesting that the target INR was somewhere around

2 to 3 in these patients, and the mean INR was 2.2 at the time of clot detection. Only 45 percent of the observations were within the therapeutic range for INR for warfarin, and nearly a fifth of patients stopped the drug before the end of the study.

Another factor that maybe wasn't mentioned much in previous discussions is when we have these kids on warfarin, it really affects their quality of life. Even going out to just play soccer can be difficult and often prohibited. So it really affects these kids' quality of life.

It would appear from this study that adequate anticoagulation is probably not achievable, at least at these doses and with these drugs, so it may require more than a single agent. And, again, as was heard over and over, clinical trials are especially difficult in this population.

There was a recent meta-analysis of anticoagulation and anticoagulate therapy following post surgery for Fontan patients. And this was recently published in Pediatric Cardiology. Among the experts in the field and the various people

providing care to these patients, there's really no consensus as to the type or duration of therapy.

Typically, most people will use aspirin in pediatric cardiology or unfractionated heparin, followed by a vitamin K antagonist, to achieve a target INR of 2 to 3. That's the currently recommended strategy. But, again, we don't know what the optimal dosages are or the optimal target INR.

It would appear, just from this meta-analysis, that the use of antiplatelet and anticoagulation therapy is combined for about six months and then followed by lifelong antiplatelet therapy. That seems to be the most commonly used strategy, but, quite honestly, we're wandering around in the dark here. We really don't know what the best approach is to these patients.

I'm not going to talk much about acute therapy. You've heard about that from other experts in the field. Chronic therapy, we've heard over and over about the issues and problems associated with warfarin.

Just a few other points. It would appear

that Fontan patients, for whatever reason, require a lower dosage compared to other patients with congenital heart disease. And many of our patients are on enteral nutrition; they require a higher dosage.

So here's what we -- "we," I'm speaking broadly for the field of pediatric cardiology, without their consent, I'll have to say.

[Laughter.]

DR. ARTMAN We would say that the characteristics of an ideal drug for our field would be age-appropriate oral formulation without long-term adverse effects, such as we heard about bone density, et cetera; without the drug-drug or drug environment interactions with many of the currently available medications; a favorable safety and toxicity profile; and to be able to easily measure pharmacokinetics and correlate that with pharmacodynamic measures. And then you've heard over and over the issues about performing a feasible randomized controlled trial that can help us inform labeling for these drugs.

So the issues and challenges, in summary, for

congenital heart disease, anyway, is that this population is growing. The children are surviving and growing up into adulthood. Long-term anticoagulation, lifelong, is often required. And you've already heard the challenges, and I'm not going to dwell on those since everyone's eager for a break.

I think the future directions in our field, there seems to be a lot of siloing between the hematologists, the cardiologists, the cardiac surgeons, and others. I think we need to break down some of those silos and do better at collaborating. One of our former presidents used to say that the right hand doesn't know what the left hand is doing, and I think that's the case in this field.

We need to develop better or exploit current biomarkers and pharmacokinetic and pharmacodynamic data. And I think it's very important to study these drugs in the congenital heart disease and cardiac surgery population. They have different pathophysiology than many of the other populations we've heard about. They have a lifelong need for

safe and effective therapy.

You heard a little bit earlier about some of the networks and resources available, and I think we'll hear more about what's available at NHLVI. But one is the Pediatric Heart Network that has been in place for about 10 years now. There are nine clinical centers, and depending upon the studies that are being conducted, they have also included some ancillary sites. There's been up to 20 auxiliary sites for some of the other studies.

So this is a network, a mechanism that's already in place for doing clinical trials in the pediatric, cardiac, and cardiac surgical population that some of you may not be aware of. And it's set up -- there's a separate data coordinating center, and it's well-poised, I think, to address some of these issues.

In the spirit of full disclosure, I am the chair of the protocol review committee for the Pediatric Heart Network. I'm not involved in designing these studies but chair the committee that reviews the final protocols.

I'd be happy to try and address any questions you might have.

Clarifying Questions from Subcommittee

DR. BALIS: Thank you. We have time, I think, for a few questions if anyone has one. And I might start off by asking, these patients, obviously, like many of the others we've talked about, are complicated, sick, undergoing a lot of procedures.

What do you think about the feasibility of enrolling them onto studies looking specifically at questions of thrombosis in the setting, hospital setting, that they're in?

DR. ARTMAN: Yes. I've thought about that a lot, stimulated by the earlier discussion. And I really think it is quite feasible, again based upon the experience of the Pediatric Heart Network.

It was thought years ago that we'd never be able to get pediatric cardiac surgeons to do a randomized prospective surgical trial, and, in fact, that was accomplished through this network recently, different approaches to the staging of the Fontan procedure. And it was a randomized prospective

surgical trial.

So the fact that the surgeons are on board with this, certainly the cardiologists are clearly coming around to this concept, and so I think it's entirely feasible. Absolutely.

DR. BALIS: Dr. Luban?

DR. LUBAN: Can you speak at all to the use of other antiplatelet agents other than aspirin in this population and make some comments, potentially, about the age span of the use of those meds?

DR. ARTMAN: Yes. It's interesting -- we pediatric cardiologists, I don't think we think outside the box very well. So it's kind of aspirin. Aspirin is probably the most commonly used in these patients. And I'm not sure there's a wealth of experience with other antiplatelet drugs.

Those issues about using aspirin in younger-age patients, there's always the concern with chronic aspirin therapy of Reye's syndrome. So there are all kinds of issues associated with aspirin, and I think that's a study that needs to be done, to look at other antiplatelet drugs.

DR. LUBAN: So if I can just add, we have a fairly large adult complex congenital heart program, and I'm finding that a lot of these individuals are coming in on Plavix and other antiplatelet other than aspirin. And as pediatric hematologists, we don't have a lot of experience with those meds. And so I think that's yet another population that bears some attention.

DR. BALIS: Thank you.

Why don't we take a break. I think we're going to do 15 minutes, so we'll be back at about 10:50. And I'll remind everyone here to please refrain from any discussion of the issues at hand here during the breaks, either among yourselves or with the audience. Thank you.

(Whereupon, a brief recess was taken.)

DR. BALIS: Okay. Thank you. We'll move on to our presentation from industry, from Dr. Portman.

Guest Speaker Presentation - Ronald Portman

DR. PORTMAN: Thank you very much. Thank you to Dr. Farrell for inviting me to come here for what's a very interesting discussion, and certainly

something that we are keenly interested in hearing the thoughts of the committee.

I am a pediatric nephrologist who was in academia for many years before moving to industry. I am representing myself. I work at Bristol-Myers Squibb, but what I'm saying here is not necessarily their opinion. And I am also the chair of the BIO pediatric committee.

These slides that I'm presenting today are not all for presentation purposes; some of them are for reference purposes that I thought would be interesting to members of the committee. So I won't be going through every single slide in excruciating detail.

All the information that are contained in the slides are in the public sector, even the backup slides, which are more detailed than what I'm going to be presenting, and you're welcome to have them and post them.

I think the key thing here is that we all have a common good in mind, and that is the fact that children need anticoagulant medications. They need

better medications than we currently have. And I think some of the failures that we've had up to this time is because we really don't have very good drugs to use in kids. They aren't going to tolerate long-term injections that have no pediatric formulations, that require a lot of monitoring. And so we need to do better, and I think we have the tools to actually achieve that.

So the properties of an ideal anticoagulant, they need to be effective, safe, and convenient. This is a detailed slide. I'm not going to go through it in great detail. But the point is, I think we're almost there. We need a wide therapeutic index. We need a predictable and consistent response.

We need a drug that affects thrombosis without substantially affecting hemostasis; that's a trick. We want a situation where we don't need monitoring or dose titration for the drug. We need minimal intra- and inter-subject variability. And we want a drug that will have a rapid onset of action, but also a rapid offset of action.

We would like a drug that's oral, but that also has other available dosage forms; I don't think we're there quite yet. And we'd like a drug, obviously, that doesn't have any off-target effects, and we all know about the past history with certain liver toxicities with drugs that are not on the market.

We want to have a half-life that's suitable for a once- or twice-daily administration, and, again, I don't think we're there quite yet. We would like drugs that don't have interaction with food or other drugs, and we're getting close.

We would like to have an available reversing agent without having a risk of thrombosis if that agent is used. And, again, I don't think we're there yet either. And I think we know that we have drugs that do not bind platelet factor 4 and that do not need antithrombin.

So on this slide, basically, I'm showing three of the new novel oral anticoagulant medications. I've not included edoxaban, which hasn't made it to the U.S. as yet, and I don't have

as much information on that. But it is a factor Xa inhibitor as well, so some of what we're going to say here is represented by the two drugs in the far left column.

So I wanted to show you this slide because I think there are particular characteristics of these drugs which are going to require attention when we come to pediatrics. If we look at oral bioavailability, for example -- I don't know if this is actually showing -- one of the concerns that we may have in pediatrics with dabigatran is the fact that it is not absorbed very well and contains some tartaric acid, which has led in our adult population to a number of complaints of dyspepsia, for a better word. And so that may be a concern for our pediatric population. The other two drugs, rivaroxaban, which is a factor Xa inhibitor, and apixaban, same mechanism, are very well absorbed.

If you look at the half-life, you see that dabigatran has a longer half-life. But remember, that's biphasic, and so it's really half of that. And apixaban has a 12-hour half-life, and

rivaroxaban, interestingly, which has the shortest of the half-lives, is the one drug that is recommended as once-daily dosing for adults.

If we look at the renal clearance, I think you see that apixaban has only 25 percent renal clearance, and so there may be some advantages there for children who have chronic kidney disease. I had to say something about chronic kidney disease because I'm a nephrologist.

[Laughter.]

DR. PORTMAN: So I got it in, okay, so we're there.

As far as metabolism is concerned, we have some concerns for children, too. With dabigatran, we have excretion by glucuronidation, which we know, particularly in the infants, can be compromised, so we have to watch that for the neonatal population. But also, for the other two medications, they are metabolized in large part by CYP34A, which we know has certain developmental expression, and particularly may be low in the neonate and may be actually higher in toddlers.

Then, finally, looking at the volume of distribution, we see that while dabigatran and rivaroxaban are total body water-distributed, apixaban is distributed only in extracellular fluid, which is great because that's where it should be. However, we have to remember that the extracellular fluid space in infants and young children is more expanded than it is in the adults, so we'll have to pay attention to that as well.

So one of the issues that's going to come up here is that what we're used to in pediatrics, and when we're taking an adult drug and moving it to pediatrics, is we like to look at what the level of the drug is in adults in the appropriate -- usually blood. And we say, okay, well, there's a correlation between the action of this drug and a certain level, and so we can kind of aim for that in pediatrics, and that should be what we're shooting for in our dosage determination.

That is not the case with these anticoagulants. These anticoagulants are dose-based and not level-based. In fact, there's very poor

correlation with many anticoagulants and what actually happens to them. We know that. We've heard it today already. You can have patients who are on warfarin who have a perfectly normal -- right in the target range for their INR, and they're bleeding; or you can have patients who will have thrombosis even though their INR may be high. And so the correlation, in general, I think with most anticoagulants, is not that strong, and I think that the new ones share that characteristic.

One of the things that we see on this slide is that there is an extraordinarily good correlation between PK and PD. This particular one is for apixaban, and we can see an extremely tight correlation between the apixaban plasma concentration and the anti-Xa activity.

Now, we've done this study in vitro in children, and basically we see the exact same relationship except when you get to under six months of age, when you actually see a greater response to a given level of apixaban for a factor Xa inhibition. So that's something we're going to take into account

in our pharmacokinetic studies. Here you can see, if we look at the INR compared to the apixaban level, that there's very poor correlation between the concentration and the INR results.

So this slide basically represents the adult studies that we have so far with these three agents, looking at the efficacy and bleeding for each of the three major indications. And these three drugs have all been approved either in the United States or Europe, and there are applications pending for all of them in both geographic areas.

If we look at the upper ones, we see the prevention of VTE and orthopedics, both for knee and hip replacement. We see that the efficacy of these three drugs is at least equal to enoxaparin in all three of them. There are differences, depending on whether you use the North American regimen of 30 milligrams Q12 or the European regimen of 40 milligrams once a day. But, essentially, it's similar or superior to enoxaparin. Bleeding is generally the same for dabigatran, is greater for rivaroxaban, and is less or equal for apixaban.

If we look at VTE treatment, we see that, in general, in the acute phase, the dabigatran and rivaroxaban are about the same as VKAs or a combination of low-molecular-weight heparin and VKAs in the acute period, with equal bleeding.

If you look at rivaroxaban with its long-term prophylaxis compared to placebo, you see what you would expect. You have better efficacy with rivaroxaban than placebo, but you also have more bleeding compared to placebo. The apixaban studies are in progress, so there's really not a whole lot to say there.

When we look at stroke prevention, we see that dabigatran was superior to warfarin in an open label model. There were two doses used there, and the higher dose was superior to warfarin with similar bleeding, so an excellent drug. Rivaroxaban showed noninferiority to warfarin, so as good as warfarin, and a similar level of bleeding. And apixaban was superior to warfarin in a double-blinded sham INR approach against warfarin and had less bleeding.

So, again, I just wanted to make the point

that in order to avoid monitoring, the clinical effect and adverse events in the adult is correlated to the dose and not to the drug level for all three of these drugs.

So turning to pediatric drug development -- and I know most of you people in this room are well aware of this issue but I just want to bring it up so that we understand exactly what we're talking about when we say we're going to develop a drug for children. Okay?

First of all, as I stated earlier, this is something that we all have to do together. I mean, not one of our groups -- the industry can't do it without academia, and we certainly can't do it without the regulatory authorities. The requirement that we have in industry is that every single drug or biologic compound that we develop into the clinical space has to have a pediatric plan. That plan may be a waiver request, that plan may be a deferral request, or it may be a full study request. But it has to be addressed, and it has to be a plan.

Now, that plan is very detailed. It's not

simply doing another clinical trial to add onto the armamentarium of the drug. It is a full development plan. As was stated earlier, we have to consult with our academic colleagues very early on in the process, and I'll show you the team that we have put together.

We have to have an age-appropriate indication. We have to have juvenile toxicity studies, or at least considerations for them. We need an age-appropriate formulation or formulations. And, as we know from the NIH conference that's going on simultaneously with this meeting, that is a daunting task to put together pediatric formulations, and it has all the steps that I've listed here that I'm not going to go through in detail.

We need to have good endpoints, which is really a challenge in pediatrics, and biomarker studies. We need to have a good way to select the dose, and using pharmacometric studies. We have safety and efficacy studies, and we need to assess whether or not it would be better for the pediatric population if we can extrapolate from the adult population to children or from older children to

younger.

We need to do long-term safety studies with many of our trials and good epidemiology studies. We need to be transparent about what we're doing, and we have requirements to make sure that these are all published not on in the FDA and EMA websites, in clin trials and EudraCT, but are also published in the literature.

Then we have to recognize that the cycle starts all over again if our adult drug has a new indication, a new dose, a new route of administration, a new active ingredient, or a new formulation. Then the whole process begins again. We have a new PREA requirement, or we have a new requirement in Europe for a PIP or a PIP modification.

So we've heard a lot about epidemiology of VTE in children, and certainly the right hand of the slide is very familiar to you. However, the left hand of the slide was a study that was prepared for BMS by Ellis Neufeld and Jane Newburger from Harvard, who reviewed the Public Health Information System,

the PHIS, for children who had been admitted from 2005 to 2007 with an administration during the admission of an antithrombotic medication, and they found 40,000 such patients; 30,000 of them were receiving aspirin, and we don't know the exact indication, but got aspirin. That was the largest. Ten thousand, enoxaparin; 6,000 for warfarin, and then the others you can see there. Interestingly, 20 of the top 25 diagnoses requiring an anticoagulant or an antiplatelet drug were for congenital heart disease.

Also, Jane and Ellis did a study for us at Boston Children's over a four-year period, looking at the number of VTEs there, and they found almost 200 children who had a VTE. And I think the important things here -- you can go over each of the diagnoses if you choose, but I think the important part here is that almost a third were catheter-related, indwelling central venous line catheter, and then, also, patients who received L-asperaginase, which over 95 percent of these also had a central catheter. So between these two, 40 percent were at least

catheter-related.

So what is the need for a novel oral anticoagulant in pediatrics? It really comes down to two categories, either the prevention of VTE or the treatment of VTE. Now, the treatment of VTE is certainly much more straightforward; if the child has a thrombosis and you can't attend to it by removing a catheter, for example, then it needs to be treated with an anticoagulant. And how that's done is something beyond the discussion today.

But prevention is, I think, even more challenging for pediatrics. We've already heard that in the adult world -- and I've gone over those prevention indications, mostly related to prevention of stroke with atrial fibrillation, or with prevention after orthopedic surgery.

But what about for pediatrics? Well, the most common cause of thrombus in kids is related to a central venous catheter. Congenital heart disease is certainly common, as we've talked, or acquired heart disease; sickle cell disease; genetic thrombophilia or acquired thrombophilia, and then once they've had

a thrombus, secondary prevention.

So we talked about expert consultation. I'm certain that most of you people in this room know at least a majority of the people who are on this list. And we went out and talked to all of these people because this was three to four years ago, and we said, we've got this anticoagulant, and we think it's going to be a major advance. How do we study it in pediatrics? What do you need? What is the need in pediatrics?

We knew about treatment. But to be honest with you, three years ago, we didn't even know that we were going to go for a treatment indication. We were really much more interested in the adult realm for prevention. So our initial thoughts for pediatrics is, what can we do for VTE prevention in pediatrics? And so we talked with all of these people to come up with our plan.

So anticoagulants in pediatrics is being addressed in Europe through the process of the Pediatric Investigational Plan. And this slide, which I'm not going to go through in great detail,

represents the core NOACs -- dabigatran, apixaban, rivaroxaban, and edoxaban -- and shows you the PK/PD studies that are being done.

Dabigatran has a three-day study in various age groups at the end of standard anticoagulant treatment for an existing thrombus, and then later has an open label study for 20 days in various age groups comparing dabigatran versus enoxaparin.

Apixaban has currently a multi-dose PK that has not been terribly successful, frankly, because of the requirements that were requested by Europe. And that's being modified to a single-dose study. But it includes all age groups for children who are at risk for thrombus.

Rivaroxaban has several -- I think three -- different studies. One of them is really two different age groups. And, again, the first study is a single-dose PK study, and the second and third studies in the different age groups are related to a four-week comparison study on children who have had two months of treatment for a VTE. And, then, finally, edoxaban, age from birth to less than 18

with a DVT who are being treated initially with standard of care.

So those are the PK/PD studies. These are the clinical studies that have been proposed in the PIPs. Dabigatran and rivaroxaban, their indication is the treatment of DVT. Edoxaban has both a treatment and a prevention study. The prevention is in cardiac disease, but we have no details on that.

The apixaban program, which is the second column, includes two studies for prevention and one study for treatment. It's not listed on this slide because the PIP hasn't been submitted yet, but we do have a treatment plan as well. The two prevention studies, one is in the prevention of catheter-related thrombosis compared to placebo, and the other is currently an open label safety trial versus VKAs in patients who require warfarin due to their congenital heart disease.

So going back to the prevention issue, if we look at the unmet pediatric need, we have already heard that adequately-powered, randomized, controlled, intervention trials of anticoagulants in

children have not been performed. There are no approved anticoagulant drugs based on clinical trials in children.

The most common association of VTE in children is the presence of a CVC, and the data on the next line of 5.3 per 10,000 hospitalizations we know now is actually much higher. It's at least 18 per 10,000 based on the study that I quoted earlier today.

As many as 73 percent of children with ALL have catheter-associated DVT associated with their induction chemotherapy. That was a study done with spiral CT, and it seems like the prevalence is really dependent upon that radiographic technique that is used to identify the clot. Interestingly, only 3 to 6 percent of these patients with the catheters have a symptomatic DVT.

However, the fact that it's asymptomatic doesn't mean it's not important because these thrombi can lead to the loss of central venous access, which we know can be critical for these very sick patients. It can lead to pulmonary embolism, or it can lead to

post-thrombotic syndrome or even superior vena cava syndrome. Currently, there is no effective therapy for CVC VTE prevention.

So I did my own little meta-analysis of catheter-related thromboses, looking at almost 30 studies with different diseases. And we can see, certainly, cancer has been the most well-studied, with 19 studies and almost 2200 patients. And in those studies we see a minimum catheter-related thrombosis of 8 percent, a maximum of 73 percent, with a mean of about 20 percent.

You can see there's also thrombosis related to the catheter in other diseases. This was done so that we could prove to ourselves that it's not simply the disease, but it's also the fact that the catheter is present in multiple different diseases that leads to the risk for thrombosis.

Now, several academic groups -- and this one, the International Society of Thrombosis and Hemostasis, or ISTH, have put together some guidelines for the endpoints that we should have for treatment studies and prophylaxis studies. This was

authored by Leslie Mitchell, who is the chairperson of our steering committee.

Just to look at the prophylactic studies, the primary outcome is all incident VTE and VTE-related mortality. The secondary outcomes are the individual components of the primary outcome, or incident PE, symptomatic DVT, asymptomatic DVT, or post-thrombotic syndrome, and the treatment studies have very similar outcomes.

If we look at the bleeding outcome, this is very similar to the adult ISTH criteria that have been well-accepted, although there are some modifications for pediatrics, and I'm not going to go through this in detail.

So one of the other issues -- the catheter program, as Dr. Artman had said previously, is the real need for anticoagulants in cardiac disease. That's clearly recognized. The problem is, what cardiac disease? What disease is actually prevalent enough that we can do a reasonably-powered study?

These are some of the candidates that we've been looking at, and we're still looking at this now:

the pre- or post-Fontan population, systemic to pulmonary artery shunt population as the Blalock-Taussig shunts, Kawasaki's disease, forms of arrhythmia, cardiomyopathies, various cardiac valvular abnormalities, pulmonary hypertension, and even thrombosis related to cardiac catheterization are some of the candidates.

This was a study. I'm not going to go through it since Dr. Artman already discussed it.

So when we look at the drug that Bristol-Myers Squibb has in this category, which is apixaban, we have a wide-ranging clinical program. And I'll just take a second to go over this program currently.

We have a range-finding and toxicity study in juvenile rats, which has been completed, and we found no findings of concern. We did an in vitro validation of the level of apixaban in relation to factor Xa levels that I mentioned previously in serum from children from birth to 17 years of age.

We have developed a formulation, a liquid, very yummy orange-flavored formulation as 0.4 milligrams per deciliter. And, actually, the

two-year stability data should be out today.

We have done a bioequivalence study in adults showing that it does have bioequivalence with the pills. And we have even -- realizing that a lot of these patients might have to get this drug through an NG tube, we did an NG tube recovery study with and without formula, and we found out that without formula, if we just chase it basically with fluid, we'd need 25 cc of D5 in order to get good recovery from the tube, which was unacceptable for infants. So we actually mixed the apixaban with formula and put it through the tube, and found we got 95 percent recovery when we did that. So I think that we'll be all set for that eventuality.

We are in the process of doing a feasibility study of radiographic tests to determine the presence of catheter-related thrombosis. In our early discussions with FDA, when the Hematology Division was actually mixed with radiology, we had a lot of radiographic interest, and they basically said, well, we would be very interested in you doing this as an event-based trial. And we said, well, 90 percent of

them are asymptomatic events, so we really need to have a radiographic study to make these diagnoses. And they said, well, that's great. We want to use noninvasive tests, as did we. But we didn't -- interestingly, there's no data for MRI, MRA, or ultrasound for determining the presence of catheter vein thrombosis. So we said, okay; let's do a feasibility trial.

So we're doing a study in 120 children to look at whether or not we can feasibly identify these catheter-related thromboses. And we've enrolled about 40 patients so far, and think we'll finish that within the year.

We have the PK/PD multiple ascending dose study, which is not an acceptable study. And just to describe it for you, this was something that, I regret to say, was really something that was insisted upon by our European colleagues, that we do a 10-day trial of giving children with catheters 10 days' worth of apixaban when it wasn't going to benefit them at all, and to do a long-term pharmacokinetic study. And, as you might expect, we enrolled one

patient.

This was not a surprise to us. I think it may be a surprise to our regulatory colleagues. But we are submitting a modification to a single-dose trial shortly, and hopefully that will be accepted because we have now a lot more modeling information than we did three years ago, and I think we have a convincing argument for making this a more feasible study.

We have the CVC VTE prevention study I've described. We have the prevention of VTE in congenital heart disease that we're working on. And, finally, we have a VTE treatment program which we are planning to propose an extrapolation of efficacy with an open label safety study and dose confirmation.

So, to conclude, the NOACs may prove to be one of the most significant innovations in clinical practice in the last 60 years. Both thrombin inhibitors and direct factor Xa inhibitors allow physicians to use these medications without monitoring, with a very broad therapeutic window, with less regard for food intake, and with limited

drug-drug interactions. And we are working, as are other companies, for a comprehensive pediatric drug development program.

Now, what are the challenges? My challenges are a little different than the challenges that have been outlined by others, not that those challenges aren't real. But the challenges I want to put forward are from an industry standpoint. And one of the challenges that we certainly face is harmonization of our two major regulatory authorities. We have already been working for two years with EEU on this program, with little input from FDA so far. And we would love to have more interaction.

Why have we not had that? Well, we really haven't had a drug yet. We haven't finished our adult program. We haven't applied for approval until just very recently. And that indication, we believe, will be waived because it's for atrial fibrillation. So that has been, I think, our holdup with FDA. But we are most anxious to discuss our program that we have and see if it's acceptable to FDA and see if we

can work together to be sure that we have a global plan.

The phase 1 studies I've already mentioned. The determination of endpoints has been discussed. I think the operations will be extremely challenging. The recruitment of patients, especially with competing trials, will challenge the success of any of them.

I've already shown you that we have four NOACs, all doing trials in the treatment of VTE. And I'm concerned, and I think all the companies are concerned, are there enough patients for four different companies to be able to do adequate trials for VTE treatment? And I think that's going to be a real challenge.

Do we need randomized, controlled trials to determine efficacy of anticoagulant medications in children? Clearly, we need safety trials. Do we need efficacy trials?

I think the answer to that is absolutely and unquestionably, yes, particularly because we don't have that correlation with the adult world of knowing

what level we should be shooting for. So how are we going to know what dose to use in children if we don't have an efficacy trial? So I think we have to have an efficacy trial. So how are we going to determine that dose? Our PK/PD studies will certainly help, as well as knowing the doses that have been efficacious in the adult population.

I think that another concern that I have, which I think is a huge concern, is that these trials take a long time to do. Warfarin is a terrible drug. Okay? It's all we've had. Enoxaparin is a great drug, but it's not really well-accepted to have all of these shots every day.

When these drugs become available and pediatricians have the option to use them off-label, and they have no other choice, what would they do? What would you do? What would I do? Well, I'd probably use them. And, hopefully, you will use them as part of a clinical trial so that we can get the data that we need. But the concern we have is that they'll be used off-label, and a lot of the subjects that would be needed to do the trials properly will

be taken up because the drugs will be used off-label, and that's a big concern for us.

So I'll be free to answer any questions.

Clarifying Questions from Subcommittee

DR. BALIS: Thank you. We have time for a few questions if anyone wants to ask. Maybe I'll start off by -- I'm saying that I think it's laudable that your development plan goes, actually, through the step of identifying efficacy, presumably, with the goal of getting an approved indication in a pediatric population.

Could you give us some insight from the industry perspective as to what drives that in children? Is it because you think the market's adequate, or is it just because you think it's the right thing to do, or what is it that moves you to extend the studies beyond the minimum of PK and safety for labeling?

DR. PORTMAN: Okay. I want to be altruistic here and say that, of course, it's something that's needed, and so that's what we're doing. That didn't work up until 1997, when FDAMA was passed. And then

finally we had a legislation that was going to stimulate industry because incentives work. BPCA works. PREA works. We want both BPCA and PREA to be passed. We think they work very well together. And we'd like to see them passed permanently in their current form. It doesn't mean there can't be some tweaks here and there. But, I mean, basically, these are drugs that work.

Believe it or not, we have legislation in this country that works. We've gone from 10 labels in the decade prior to FDAMA to 400 since, or more. I mean, they work. And so that's the driving force, that and the EMA. That's the driving force for doing this.

If we're going to do it, frankly, we're going to do it right. And that has been the attitude of our company. If we're going to do these pediatric studies, then, by God, let's do them and make sure that we're going to do it and we're going to get valuable information. Because what's the point otherwise? And that really has driven it.

DR. BALIS: Great. Thank you.

Dr. Young?

DR. YOUNG: Yes. I'll just add that from the non-industry perspective, that I completely agree that the driving force is the incentives and the requirements that come from regulations because, as you saw in my presentations, I would go begging and pleading drug companies to fund these studies.

My first try, two of three said, no, we're not going to do pediatrics. We don't need to. We're not interested. One of them did. Honestly, it was completely altruistic that they did it. They didn't have to do it.

Then, going forward, it was the same issues over and over again. No, there's no market. We're not interested. And then, when the EMA passed their new regulations, then suddenly a whole new world opened. And now, all these companies, they have to have these very detailed pediatric investigation plans submitted, actually, even, as part of their application for licensure.

So I think that it's nice to have some laws that actually do what they're intended to do. And I

think, really, that's the driving force. As much as we'd like to think companies are doing it for altruism or -- it's certainly not for market share, that's for sure. But the regulations work, and we hope that those regulations continue, because it helps us to get funding.

DR. BALIS: Great.

Dr. Kaskel?

DR. KASKEL: Is this working now? Okay.

Ron, we saw two weeks ago at that meeting about the recent RFA about biomarkers, development of biomarkers in pediatric trials. Here's an example where, potentially, industry and academia and government support could merge to look at some new biomarkers.

DR. PORTMAN: Absolutely.

DR. BALIS: Thank you, Dr. Portman.

So we have our last presentation from NHLBI, last before lunch. Dr. DiMichele, can you introduce yourself, too, please?

Speaker Presentation - Donna DiMichele

DR. DIMICHELE: I will.

DR. BALIS: Thank you.

DR. DIMICHELE: Hi. My name is Donna DiMichele, and I'm the deputy director of the Division of Blood Diseases and Resources within NHLBI. Just by way of background, I'm a pediatric hematologist, and hemostasis and thrombosis was my area of interest and my area of research when I was in academia. Also, I am the acting director of the Thrombosis and Hemostasis Branch at the moment.

So, initially, I have a very short presentation, I'm going to go through this very quickly. The original aim of this presentation was to tell you about the resources at NHLBI that are available to help further this mission of trials in pediatric thrombosis and pediatric anticoagulation. A lot of the stuff has already been mentioned, so I'm going to try to expound on it and also collate it into an overall program that we think we have that might be useful in this regard.

So I'd like to divide the talk into three areas in which we think that we have resources. First is that of clinical trial planning and

execution through various funding options. The second is research infrastructure for clinical trials, a lot of which has actually been mentioned so far, and I'm going to tell you a little bit more about that; and then something that we haven't talked very much about, and that is ancillary clinical trial support mechanisms that we think might be also very important.

Now, with respect to clinical trial planning and execution and funding support, although I'm talking on behalf of NHLBI, a lot of those mechanisms actually come through the Division of Blood Diseases and Resources, and specifically through the Thrombosis and Hemostasis Branch. But there's one program that I'm going to mention, the R34 pilot, that is an NHLBI-wide effort.

Now, before I go into that, I just want to say that through the Division of Blood, what I'm going to talk about is on a background of a wide range of research support that we offer in terms of various types of trials -- observational studies, technology development and training -- that is

largely investigator-initiated. And, actually, it works very well to advance the field of thrombosis and hemostasis.

But let's talk a little bit about what we've done in the way of RFAs. Certainly the issue of deep vein thrombosis and anticoagulation, whether it be in adults or pediatrics, is very much within the mission of DBDR within NHLBI. And an RFA that was initiated in 2008 and will end in 2013 has supported eight R01 grants that are looking at various aspects of VTE.

If you look at point number 2, the initiation of clinical and translational studies to improve diagnostic therapy, that one is very much related to, certainly, anticoagulation and anticoagulation trials. And Guy Young referred to this RFA since his pediatric anticoagulation trial in bivalirudin is actually one of the R01 grants that's actually funded through this mechanism. So certainly RFAs, general RFAs in thrombosis, is one way that we have to further this mission.

Now, I just want to mention also, this is an NHLBI-wide resource, which is the R34 pilot trial

program in these applications. These are smaller grants, 450,000 over a three-year period with separate review mechanisms and the ability to apply for these three times a year. And what this program is meant to do is to actually look at clinical trials and actually do pilot studies to ascertain the feasibility of moving forward with a full-scale clinical trial. And these have been, actually, very, very successful grants in terms of doing some of the background work that's required to move studies, particularly studies that are difficult to do, forward.

On the other hand, this mechanism does require that there be a pilot trial and pilot data. And so one of the things that we've recognized is that there needs to be a further mechanism because there are trials in which a pilot-sized trial is the trial, and in which -- these are trials in rare diseases, and these are very, very difficult-to-do trials.

So, therefore, following upon the recommendations of our State of the Science Symposium

in Transfusion Medicine and Hemostasis/Thrombosis that was held in September of 2009, in which one of the recommendations was to develop programs to encourage clinical trials for rare bleeding and clotting diseases and for studies in pediatric populations, including processes for planning, initiation, and successful completion of trials, we took that to heart and, indeed, developed yet a third program, which was basically initiated this year. And that is the U34/U24 planning grant RFA, which is specifically for planning clinical trials, particularly for those diseases, many of which are hemostasis-related. But we included pediatric thrombosis in this because these are trials in rare diseases, as we said, in which the pilot trial would be the trial.

Specific planning with respect to building specific networks, getting the resources that are needed, designing the trials, acquiring drug in certain instances, getting and working with FDA to get the IND, these are all aspects of the trial that are very critical to completing it with success, and

usually even within an R01 mechanism require the first one to two years of an R01 to actually succeed in doing -- in this case, these grants are specifically to plan these very difficult-to-do trials.

Again, these really touch upon many of the things that we've talked about today, and that is both rare disorders, of which pediatric thrombosis, although it's increasing, is certainly still rare; and also trials that are very, very difficult to do because the people doing the trials actually aren't the primary caregivers for the patient population.

Now, the U34, as I'm trying to explain, is rather similar to the R34 in terms of its duration of support and level of funding, et cetera, but it is focused on rare thrombotic and hemostatic disorders. And it is combined with a U24 clinical resource, clinical trials resource, that, actually, the U34 applicants are going to be required to tap into. And, again, the collection of preliminary data is not required in this mechanism. There are set-aside funds to fund 10 applications over the course of

three years, and we actually had our first application due date in October, this past month.

Now, a little bit about the U24. And, again, this program, the uniqueness of this program, is that these planning grants are actually working together with a clinical resource that is a separate application for this clinical trial resource in which academic institutions, schools of public health, commercial organizations, and, specifically, CTSAs have been encouraged to submit applications to become that resource in which they would have all of the tools needed to advise these individuals on how to conduct these trials. And this is a single submission date, and, again, those applications were just received in October of 2011.

So on to the infrastructure. And, basically, I'd like to discuss two separate things. And, again, I'm going to go through these very quickly because all of this infrastructure was already mentioned.

As some people said, we need a pediatric hemostasis infrastructure in which to conduct these trials. But I think we would suggest, and Dr. Shurin

has already commented on this, that there are already established research networks that we can actually leverage in order to do some of what is being discussed here. One of these is an NHLBI-based research network. The others could involve some trans-institute collaborations.

The one NHLBI resource is the Pediatric Heart Network, which has already been discussed. Again, nine centers, lots of ancillary sites, a data coordinating center; it's a national network of pediatric cardiologists and cardiac surgeons. It's a 10-year-old network, and you can see that over that 10 years, they have done several clinical trials, circled in red, and observational studies, two of which have actually been in Fontan cohorts already identified by other speakers as significantly in need of pediatric thrombosis trials. So the issue of thrombosis in pediatric cardiology and in cardiac surgery has, as has been said, become an issue of significant importance. And this is a potentially very good network with which to partner.

In addition to that, we have networks, two

networks that Dr. Shurin alluded to, in NICHD. One is the Pediatric Critical Care Research Network, which is eight centers, seven sites. You can see those here. They basically encompass 17,000 pediatric ICU admissions per year, and combined with the Neonatal Research Network, which also involves a large number of centers that specifically deal with NICU admissions -- there are 33,000 there that are represented -- and do research in neonatal conditions, these two networks are critically important, we would think, to furthering trials in pediatric anticoagulation largely because, as people have already mentioned, from an epidemiological standpoint, this is where a lot of the pediatric thrombosis is occurring.

Pediatric thrombosis is an inpatient disease, largely, involving critically ill infants and children, and these critical care networks -- which, by the way, are very, very interested in procedures such as ECMO -- would provide actually excellent infrastructure, we think, for pediatric trials.

Now, I haven't mentioned, of course, NCI's

Children's Oncology Group because I figured that was quite familiar to most of the people on this panel, and that actually is another resource.

Now, also within NICHD, I'd like to point out that they have a relatively new mechanism, the Pediatric Trials Network, that has arisen out of the Best Pharmaceuticals for Children Act, which actually is a mechanism to provide infrastructure for pediatric clinical trials, specifically with respect to doing PK/PD formulations development and, certainly, device development, which I think, again, is a very important resource to leverage in thinking about moving forward with pediatric anticoagulation trials.

Now, in the last few minutes that I have, I just want to mention some of the things, some of the ancillary support mechanisms, that haven't been discussed very, very much. And I'd like to talk a little bit about our BioLINCC, Biorepository; the SBIR program that we have for technology development, which we think is very, very critical to moving this field forward; and of course, training, since we need

the investigators to do this work.

The BioLINCC and Biorepository is an NHLBI resource that currently has over 4 million samples, whether they be plasma, serum, cells, or tissue specimens, which are available to investigators. These are, by the way, samples that are very well clinically phenotyped; that's where the BioLINCC comes in. This is a resource that's run by an external company, one of our contracts with SeraCare, and these very well phenotyped samples are now made available to investigators through just general and through some specific mechanisms to access and with which to do research.

Where this is very important, you can see, is, for instance, as trials are being done -- especially trials through NHLBI, we do have data sharing agreements. And these data sharing agreements can include taking over these specimens -- again, very well clinically phenotyped specimens -- on which other studies can be done, thereby maximally leveraging any samples that are collected in pediatric trials, pediatric trials of

thrombosis or in anticoagulation.

In addition to that, we have some specific initiatives, like R21 mechanism RFAS, that have actually been specifically developed to maximize this resource, to maximize the exploration of these resources for further research.

Finally, I just want to mention the SBIR and STTR program because, again, it's been alluded to in this meeting, but there are many barriers to doing trials in pediatric thrombosis and pediatric anticoagulation. A lot of them have to do with technical aspects.

We've mentioned how difficult it is oftentimes to diagnose clots in children. We've talked about drug formulations and the applicability of formulations for adults, or the nonapplicability for children. We've talked about the fact that in doing these studies right now, you still need 3 mls of anticoagulated blood to do some of the sampling, and the need for microtechnology -- microassays, microfluidic technologies -- in the application to these trials.

This is where we think that our SBIR program is very, very important. And, in fact, not only do we think it's important, but we believe it needs to be expanded in mechanisms that are coming on board. I don't have a lot of time to explain right now, but that will be very useful in partnering with industry to create the technological advances that we need to do pediatric anticoagulation trials. And we are developing mechanisms within NHLBI to also target our requests for SBIR submissions that we think will also be very useful in this regard.

Finally, I just want to talk about training. We're still very much in the training business, and training at all levels. And as has also been alluded to, the need for pediatric investigators, not only in hematology but in cardiology, nephrology, and many of the specialties that would be vested in proceeding with pediatric anticoagulation trials, we think that certainly from the standpoint of training hematology, we have a major role, and we still have many mechanisms to do this.

I also just wanted to mention, although we

have the R34 pilots, one of the mechanisms that we haven't advertised so much as another pilot mechanism to do trials, in which we actually have two of these going on right now, is our K23. It's a training program in clinical science. And, actually, we have two investigators, one of whom is going on to an R01, who are looking at studying two major questions in pediatric thrombosis that have actually been mentioned at this meeting. One is catheters, the role of infection and inflammation in catheter-associated thrombosis, and another in duration of therapy, optimal duration of therapy, in preventing recurrence of pediatric thrombosis.

These are two studies that are being piloted through the K23 mechanism, which has also, I think, been very fruitful in trying to develop careers in pediatric thrombosis.

With that, I think I will end, and thank you for your attention.

DR. BALIS: Thank you.

Clarifying Questions from Subcommittee

We have time for questions if anybody has any

for Dr. DiMichele. Yes, Dr. Freedman?

DR. FREEDMAN: Thank you for that presentation. I just wanted to know what amount of dollars are actually available for your program for the extramural component. In other words, how much is actually allocated to grants per year?

DR. DIMICHELE: Well, I don't think we can tell you that, but maybe I'll let Dr. Shurin --

DR. SHURIN: I can tell you that none is. Nothing is allocated. Everything is issued on the basis of how well things do in peer review, with attention to portfolio balance. So except for the RFAs, where there are set-aside funds, everything comes in in competition with other applications.

DR. FREEDMAN: Yes. Because I've served on the National Cancer Board, and I know how these budgets are worked out. But the problem is -- the question comes up, can the NIH and the NCI adequately support the type of trials that we're talking about, given what we know of costs to do these studies.

DR. SHURIN: No. And I think that's one of the key issues, is that the various components need

to be stapled together to make something that will be supported. We took a cut in our budget this year. We're looking at a cut this coming -- the current year. We're anticipating a bigger cut next year. By the end of this month, we may be down 7 percent.

The key issue is that we do not have the resources to set aside for this kind of program as well as for all of the others. The amount that needs to be supported is simply too great across the board. Therefore, what we do is -- it really comes back to my earlier comment about the importance of having this driven by the scientific questions, that the compelling questions and the importance, both from the standpoint of the scientific opportunity and the public health need, needs to be really eloquently put out there so that people can see these as opportunities for investments.

But my expectation is that the NIH will be one of the sources of funding, as it is for the Children's Oncology Group. But the Children's Oncology Group some significant time ago, realizing that it was going to have to supplement those funds

with other funds, has for a very long time really run, not in small part, on the fact that there is institutional investment.

I don't see this is going to be any different. And I think that's the key issue, is that without some organized leadership and a clear, strategic enunciation of the importance of this, it won't go where it needs to go.

DR. FREEDMAN: Yes. Because a problem, too, with some of these things, there are program announcements which have no budget attached to them. And that happens frequently, and in the --

DR. SHURIN: And we're doing more. And we're doing more.

DR. FREEDMAN: And then with the RFAs, it's got a defined lifespan.

DR. SHURIN: They all have a defined lifespan. Everything has a defined lifespan.

DR. FREEDMAN: That's the -- and I think right now we're looking at such a small percentile of support.

DR. SHURIN: Correct.

DR. FREEDMAN: So it's --

DR. SHURIN: That's why it has to be very compelling. That really comes back to the issue of the strongest focus on the science. The NCI supports a lot of infrastructure; we support relatively little. But I think Donna just gave a beautiful summary of much of the infrastructure that we do support. But our priority has always been on investigator-initiated research, and so 75 percent of our extramural dollars go to investigator-initiated research, as opposed to 45 percent at the NCI. And the difference is the amount of money that goes into infrastructure.

DR. BALIS: Yes, Dr. Kaskel?

DR. KASKEL: So if I was going to take a step further and say, let's try and plan something, taking advantage of all the information and the existing infrastructures, to target appropriate anticoagulation therapy in the different disciplines and age groups, I would start with some of the existing talent, not only that we've heard about today but with the networks that are out there. They

need to be harmonized under one umbrella, at least representatives of those networks. The Pediatric Trials Network is a very good starting point; the CTSA, the CC-CHOC component or the CTSA, to take advantage of the 49 CTSAs. There are 60, I think the number is, now; even representatives from the National Children's Study, because you have newborns there.

I mean, you can go on and on. But this has to be harmonized. Not an easy task. And a committee has to be formed representing all the different partnerships to come up with a plan so that, potentially, a funding opportunity could arise for competitive grants addressing this across the institutes and across the disciplines. That's the only way I think you can get at this. Very easy to say this; very hard to do.

DR. BALIS: Dr. Luban?

DR. LUBAN: And I think you could argue it's not only for anticoagulation, it's for other rare diseases that we're dealing with as well. So it's not only for one disorder, it's for other hematologic

and other disorders as well.

DR. MINNITI: Who's going to harmonize it? I mean, which structure can be so powerful and knowledgeable to harmonize this list of organizations? I don't know the answer to this question.

DR. BALIS: Yes, Dr. Reaman? He's the person.

[Laughter.]

DR. REAMAN: I'm not going to harmonize it. I'm done harmonizing, thank you very much.

[Laughter.]

DR. REAMAN: But I think no structure is going to harmonize this. I think it's going to take an individual or a group of individuals with the interest, the passion, and the leadership skills to put this together. Because I think what we've heard is that no one institute, no one organization, is really going to support this. It really does have to be pieced together. And I think utilizing the CTSA structure will be great, but I don't see anyone emerging within the CTSA who's particularly

interested in just anticoagulation. But if there are people who are interested, then I think using that structure and others is how it's going to happen. It's not going to be an organization that comes forward and says, do it this way. It's really going to require individuals to have some vision and go out and put this together.

DR. BALIS: Yes, Dr. Shurin?

DR. SHURIN: Well, I think one of the key issues, one of the things that we often do, is to try to have workshops to set the priorities. For instance, we did one in pediatric pulmonary disease a couple years ago, and came out with sort of a strategic plan, and overview. There's no plan that comes out of that that says who's going to do it, because it's all over the board. Asthma's different from bronchopulmonary dysplasia and all; but at least to sort of enunciate that so people can hang onto it.

The importance of leadership, I would really, really emphasize -- the two key things that make things really work are an organized investigator community and a benign dictator in the leadership

because somebody has to make decisions. If you make all the decisions by committee, they tend to be really unexciting. Okay? And then they don't do well in peer review because where you got to that is nobody disagreed with it, and therefore everybody's sort of willing to do it. That isn't compelling when that comes across as a scientific issue.

So it is, in fact, significantly complicated in terms of putting things together. I think it will still be a series of loosely coupled systems, and I think many of the groups who are capable of facilitating that are represented at this table. But it's not -- we've had experience before in investing and sort of saying, okay, this area really needs something, and then what I just mentioned in terms of a really powerful sense among the investigators is lacking, and it doesn't happen.

DR. BALIS: Dr. Young?

DR. YOUNG: So I told you about the grants that I've received. Now let me tell you about the grants that I have not received, despite applications.

So, as a hematologist, although hematologist/oncologist, I've viewed the COG network with a lot of envy. The culture that was brought up before, that's important. It's as important, if not maybe even more important than the funding because you have to have that culture there.

So I've made an effort, organized a group of United States experts, some of which you saw in Dr. Portman's slide, others who've been collaborators with me, and we did try to get funding to have a pediatric thrombosis network for infrastructure and to start things. And it scored okay, but it didn't score well enough to get funded.

More recently, the same group looked at -- there was a funding mechanism from the CDC for thrombosis surveillance, to try to get a handle on the numbers, because we have some of these studies but nobody really knows what the numbers are. And it was a really comprehensive application. It was put together with not just myself; I led the effort, but there were epidemiologists and others on this grant.

I'm not sure how the CDC exactly operates

with their funding, but they said, we've been approved for funding but we don't have any money right now. So that's another situation where we tried to form a network, and yet they said, well, if we get money in the next year, and we all know that's not going to likely happen, that will get funded.

So there have been some efforts, and there is a core group of pediatric thrombosis investigators, mostly hematologists, but I would echo what Dr. Artman said, that we really need to just break down the silos and not just have hematologists on that group. We should have cardiologists, neonatologists, other experts, as part of that.

So, yes, it's something that's needed. There are people in the community like myself and others -- I'm not the only one who could lead an effort like this -- to try to get organized. And we've tried, and we'll keep trying. And I'm not sure how else we can try to get the funding to do that together.

DR. BALIS: Dr. Reaman?

DR. REAMAN: I think some of the

trying -- and I'm not sure there have been many efforts. But I think requesting support to develop a new infrastructure these days is fraught with great difficulty. There's lots of infrastructures, and I think the real key here has to be looking and thinking somewhat out of the box to leverage existing infrastructures to do this.

So using the cardiology network, using PCARN, using the CTSAs, and maybe even using COG -- I can't speak for it any more, but there are certainly cancer control studies that could be considered with catheter-related thrombosis.

So I think getting interested investigators to use existing infrastructure and resources is really the way to do it. To apply for a new infrastructure and to develop one more data center and operations center, I think those days are long gone.

DR. YOUNG: Yes. I don't disagree with that. And when you don't succeed a couple times going in that direction, you realize that that's probably not something that probably will succeed.

The concern I have, though, when we talk about some of these other mechanisms, we talk about the Hemophilia Treatment Center Network, well, you know, a lot of those people, though, are really just interested in hemophilia, to be honest. Not all of them are interested in hemophilia and thrombosis. When we talk about the CTSAs, there's competing agendas and things.

So I'm not saying -- I mean, I'll take that advice and see what we can do to try to leverage some of the existing networks. But that'll be challenging, too, because there's competing agendas. But it's worth --

DR. REAMAN: There's either competing agendas or there's competing for dollars. So there's always competition.

DR. YOUNG: Anyway. Correct. Correct.

DR. BALIS: Okay. Great.

Why don't we break for lunch? We have a scheduled open public hearing afterwards, but as far as I know, we have no registrants for it. So I think maybe what we'll do is, if there are other burning

questions for the speakers, because towards the end, we didn't have as much time, we'll take a few minutes and discuss that before we get on to the questions from the agency afterwards.

So we'll be back here at 1:00. And I want to remind you all again, obviously, please don't discuss issues that -- the topic of discussion here today during your lunch break, and we'll see you back in an hour.

(Whereupon, at 12:02 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:20 p.m.)

DR. BALIS: All right. So I wanted to, before we started with the questions, continue our discussion if there were other specific questions for the presenters this morning that people wanted to raise or other comments they wanted to make related to other discussion we've had. Once we move into the questions, the discussion is a little more focused in terms of what we're going to talk about, not that we don't branch off from that.

So are there other issues or questions that anybody wanted to raise? Yes, Ms. McMillan?

MS. MCMILLAN: Hi. I'm here as a subject advocate. I have a question. In my experience with -- my son had a malignant brain tumor, so he went through a long clinical trial process. We're 15 years out; he's healthy now. But I know there was use of heparin way back when, and with the many hundreds of families I've worked with in the last 10 years, I know that all the kids have been on some kind of anticoagulant therapy at some point or

another for different reasons.

I want to know, are there long-term issues, I mean, once we're actually out of treatment phase, with the use of these kinds of drugs? And if so, what are they? And if so, you might consider harnessing some parent energy behind promoting the concerns for promoting these drugs.

DR. BALIS: Guy, do you want to take that one?

DR. YOUNG: Sure. And I can say this because this was on the cover of People magazine at some point. But I got a call from Dennis Quaid's lawyer. I don't know if you guys know this story. Dennis Quaid's twins both got inadvertent overdoses of heparin. And the main question he was concerned about is, is there going to be long-term damage to my new babies?

When I said, well, did they bleed? Was there anything -- because I didn't hear -- obviously, I wasn't taking care of them; they were in a different hospital, thank God.

[Laughter.]

DR. YOUNG: So I said, well, if they didn't bleed and they're okay now and the heparin has been neutralized or out of their system, then from that one inadvertent overdose, there shouldn't be any long-term effects.

So that's for the short-term. So the main thing we always worry about with the anticoagulants is bleeding, because bleeding, especially into the wrong place, is bad. And then, of course, I think the issue of quality of life came up, which is important, because if you're on an anticoagulant and you're trying to avoid bleeding, there's quality of life issues. You can't do this. You can't do that.

But to address your specific question about what are the long-term -- so we know chemotherapy, right, chemotherapy has lots of potential late effects. It's a huge and important area of study, is looking at adult survivors of childhood cancer and what long-term effects they have from their drugs.

What about long-term survivors of childhood thrombosis with respect to drug-related toxicity? And I kind of brought that up a little bit in my

presentation. My big concern is -- enoxaparin is the number one-used anticoagulant. We know from in vitro studies and some in vivo studies in pregnant women and some in other populations, including cancer patients, actually, that it does have a negative effect on bone density. So in other words, it can cause osteopenia/osteoporosis, thin your bones.

In adults, they only use enoxaparin -- the indication is 5 to 7 days, 10 days, 2 weeks, something like that. But in kids, I've had kids who have been on it for three years. I've had patients, lots of patients, who have been on it for six months to a year.

Now, if you add that to the fact that these are growing children, right -- their bones are still growing. They have a bone plate, basically, that's still developing so that they can grow -- what are the impacts on the growing skeleton or the immature skeleton with this drug or this class of drugs, the low-molecular-weight heparins? It's really unknown.

I've seen a few situations now where I've seen pathologic fractures. These are fractures from

thinning of the bone. But that's the extreme. What about all these kids? Are these kids, when they're turning 40 and 50, going to have osteoporosis? Because what's clearly known is that your peak bone mineral density, the most bone that you get in your body, is about the age of 18 to 20. And how much you have is directly related to your risk for osteoporosis. So if you don't build enough bone during your childhood, you have a much higher risk of osteoporosis later. That development of bone is critical during that time.

If somebody's been on low-molecular-weight heparin for six months, a year, two years, at the age of 11, 12, 13, 15, maybe even younger, what is that doing long-term? And that we don't know. I think, for me, that's primarily probably the long-term concern, is the effect on bone. So that's kind of a long answer.

DR. BALIS: Yes, please, go ahead.

MS. MCMILLAN: And one other thing is the age ranges of studies was mentioned very early on today, considering pediatrics up through age 16 and then

maybe adults 18 and on.

But, for example, my son and some of the other children that I've worked with, it seems like their puberty has been delayed because maybe whole brain radiation is damaging your pituitary gland, and we had endocrine issues.

So doesn't that change their chronological age of being considered a pediatric patient, especially with regards to some kinds of drugs? Maybe you can explain that to me. I'm worried that some child physiologically at age 16 or even age 20, still, is younger than that in terms of puberty.

DR. YOUNG: Well, I think that the one area that that further raises concern is, again, the area of bone because endocrine issues -- the bone metabolism is directly related to hormonal regulation. Hormones regulate bone, a large part of bone development. And so if you're having endocrine issues as related to chemotherapy -- and some of the drugs we use we know affect bone; I mean, steroids are the worst of the offenders -- that may actually even compound the effect of the anticoagulants. We

don't know. Sometimes we have two things that are negative, and you put them together, they actually neutralize each other. But most of the time they at least add -- one of the effects is additive or sometimes it's synergistic.

In terms of the metabolism of the drugs, that's more related to the maturity of the kidney and the liver, which is mostly where things get metabolized. And we have kidney experts here, so I'm not going to talk any more about that, and I can let them answer how, if there's some pubertal maturational differences, does that affect kidney or liver issues. I don't really know. I don't think so, but I can let them answer that.

DR. BALIS: Dr. Kaskel?

DR. KASKEL: I was going to comment about the steroids and bone. When you accrue bone, many of the conditions that we take care of, at least with the kidney disease, as in the other patients who require steroids, immunosuppression; and they have an adverse effect on bone, so that would work together to have a deleterious effect. And we do know that in the

children who make it into adulthood with kidney disease, they have increased fractures, especially the females, when they're young adult females.

In terms of the kidney function, the maturation and clearance, this is a very important area. As we've seen, some of the clearances will depend on the age of the patient. So especially at puberty, depending on the growth spurt, if they're having an active growth spurt, this is something to consider.

Often, though, in response to your question, some of our patients have delayed puberty, delayed onset of puberty, with chronic kidney disease, or even normal kidney function but with a condition causing them to lose a lot of hormones in nephrotic syndrome, and those patients, because of the nephrotic syndrome, are at risk for thromboembolism.

I'll also mention about the undue burden of having heparin given. If we have a dialysis patient, some of the young infants on dialysis, or children, are receiving it five days a week, heparin, to have the treatment. Some children are on peritoneal

dialysis, and they get heparin via the catheter every night into the peritoneum. We have no data on the long-term effects of this heparin administration in that population. Again, numbers are small. It's a rare disease, as we're talking about today. These are all rare diseases, but need to be addressed.

Questions to the Subcommittee and Discussion

DR. BALIS: Okay. If no other questions, let's move on to the specific questions we have as a committee to address.

The first one is, we've discussed a little bit this morning, the survey identified a number of challenges to successful conduct of anticoagulant trials in a pediatric population. Those challenges included difficulty in accruing patients, inadequate funding for running trials, lack of central and institutional infrastructure to organize and run the trials, and a lack of coordination between subspecialists required to do these studies, since it occurs in different groups of patients.

So the first part of question 1 that we need to address is to discuss the impact, if any, that

these issues have on the development of anticoagulants for use in pediatric patients, and to provide some suggestions for practical solutions that may address the issues that we consider to be important.

Maybe we can start with go back to these bulleted statements. There were a number of issues raised this morning about slow accrual; in fact, I think almost everybody who stood up and talked to us this morning, that was pretty high on the list.

I think slow accrual gets down to a number of issues, starting with just the sheer number of patients with the condition. But when we write a protocol, we carve out a piece of that population based on our eligibility criteria, and sometimes, at least in one instance, we heard that actually may have been the limiting factor.

Then, after that, we get to the issue about willingness to participate on the family's part and the physician's part. So it takes two to put a patient on the study. The physician has to be aware and willing, as does the family, as becoming a

research subject.

So there are a number of steps we have to go through, starting with the overall population, in getting to a patient on study. And I think it may be important to identify, if it's not all of those specific sites, where the issue is that explains the slow accrual to these studies.

So, Dr. Young, do you want to, from your perspective, give that a shot as a starting point?

DR. YOUNG: Sure. Where to start? So I think study design is critical. As I mentioned with the first round of that argatroban study, is the way that the inclusion and exclusion were written, it almost -- the exclusion excluded everybody that could be included, basically. So you have to really think about that.

This is where I've had to work with industry because they have certain exclusions that they bring from their adult studies. And I said, well, you can't exclude everybody that's got some sort of chronic disease because then you'll exclude every kid, practically, with a clot.

So I think there needs to be some real thought into clinical trial design so that you can design something where, yes, it's going to be as safe as it can be, right -- you don't want to include people that are likely going to have an adverse event – and, yes, you want it to be as defined a population as you can so you can at least generate some meaningful results. But then you don't want to have it be so specified such that, A, you can't accrue patients, and, B, then the results aren't really that generalizable anyway.

So it's just a matter of being open-minded about clinical trial design. I think that one size doesn't fit all. And I think that clinical trialists and statisticians are really focused on having things designed so explicitly and perfectly, so that when the review comes up or when the data is completed, the data accumulation, that there aren't really questions about what happened with the study design and the patient populations. But the narrower and more perfect you try to make the study, the less likely it is that you're going to be able to accrue

patients to the study.

So I think there needs to be some flexibility there to try to get as many patients at least starting out -- you want to start with the biggest pool possible. So the biggest pool possible, yes, you have to still think about safety. Still have to think about -- at the end of the trial, you need to answer the question. Right? So if you make it too big a pool, it's too diverse, or patient population is every kid with a clot with every type of catheter in every kind of disease, that might get to be too difficult to really get results out. But making it too narrow has its own problems.

In terms of funding, there's definitely been a shift. There was the time that I presented the trials that I did where it was just extraordinarily difficult to actually get any kind of funding, whether it was from industry or federal grants. And we've seen from Dr. DiMichele's presentation that there's definitely opportunities, more opportunities. The U34 is a great example of where there is funding that is -- it actually says in the RFA, pediatric

thrombosis. I don't think I'd ever seen that in an RFA before. So I was encouraged; okay, they're really interested in this.

Then the other shift is with the EMA regulations and somewhat, as well, the FDA with the BPCA and PREA, industry now, they have to do these. And with the EMA regulations, they really have to have a whole development plan. So there's a lot more funding now. And all of industry -- you heard from one representative, and you saw the other drugs that are listed up there -- they're all now conducting these pretty elaborate pediatric development plans.

The problem with some of my trials, it's a one-off. You know, you do one, and then it's like, well, now I'm going to try to get funding to continue, but you can't, or you don't. So that shifted things for the better. So I think funding, there's still not as much as we would all like. And just because I submitted one of these U34 applications doesn't mean I'm going to get funded. As you saw, only 10 are going to get funded over three years. But I think that's gotten a bit better.

Lack of a central and install infrastructure. So there's definitely a lack of a central infrastructure, and we've talked before about nobody's going to make a new network; let's leverage what we have. And I think that's an area that we need to explore. And it does have to come from, I think, the academic leadership, people like myself and the people who Ron Portman put on that list as well who are working with apixaban, to drive that. I agree with Dr. Reaman. It's really up to us. We need to drive that. The academics need to drive that. We need to come together and say, here's what we want to do, and then have a plan, and then at that point try to seek some funding to support the plan.

In terms of institutional infrastructure, it varies tremendously from institution to institution. And I don't know how that potentially could be overcome. Some institutions have a CTSA. My institution, I'm fortunate. We have a CTSA. We have lots of other support, lots of other mechanisms for funding.

I have four people who just work on clinical

trials: two research coordinators, a research nurse, a research lab person. That's it. And so I'm able to do some of this stuff because I have that support. But when I get some of my colleagues to participate, they're like, well, I don't have this and I don't have that, and I don't have the funding for this. So that's very variable, and I don't know how you would fix that.

Lack of coordination between subspecialists, that's a problem, too. Right? So we have the cardiologists, and they're doing some trials on their own, and the hematologists. And I like how Dr. Portman, again, showed that their steering committee is multidisciplinary. And I think that that's an area where I think we want to work together, and it's just a matter of finding a way to come together so that when we form these committees or we form these groups, we make sure that we include the variety of disciplines that are represented here.

So that's my take on trying to answer those.

DR. BALIS: So your answer is yes. Right? To all of those things, I mean, being issues. I

think more or less to all of those.

I think the last one, the lack of coordination, relates back to the issue of accrual. It depends on what the population is that you're doing the study in. I think some of these are early studies -- and I'll relate it back to what I know best in cancer. When we're looking in phase 1, we don't care about diagnosis. We're looking at dose and pharmacokinetic issues, which is probably also the case here. The initial safety and pharmacokinetic studies, it may not be so important precisely what the underlying condition is as long as there's an indication for the therapy.

But as you move along, you may be getting into trials that are more specific for specific patient populations with underlying diseases, where the coordination may not be as much of a limitation in the sense that there's clear buy-in from the subspecialists that they need that specific therapy for that condition. So that part may be very trial- or phase-dependent in terms of where you are in the development of the drug.

Other comments? Dr. Reaman?

DR. REAMAN: I would just say I certainly agree that study design is important. But I think, again, study design in accruing patients, I think you also have to think about the indication for which -- or the question that you're asking and in what specific patient population.

So you can have a study that is open to all comers, but we have discussed earlier today that there's great heterogeneity within this group of patients with thromboembolic disorders and conditions. So I think study design has to really start with what are you trying to accomplish and in what specific clinical situation in the patient population? So that should really drive your accrual planning and accrual expectations.

DR. BALIS: Dr. Luban?

DR. LUBAN: So getting to this lack of coordination between subspecialists, I'd like to add one group of subspecialists that we haven't approached or even discussed, and that's laboratory medicine, because for many of these studies to move

out of a research setting and into clinical use, you need to have assays that are microtized, easily available, and in some cases available 7/24, preferably on automated instruments that will allow for the safety margin of the administration of the med.

I personally think that this is one area where we don't have enough advances to really be able in the future, unless everything we use is an anti-Xa, to be able to feel secure along those lines. A PT and a PTT or even an INR isn't necessarily going to be the answer. And even when you look at PT, PTT, and INR, you're looking at standard deviation variability, instrumentation variability, and, for some of the measures, inadequate, premature, and neonatal normative values.

DR. BALIS: Dr. Shurin?

DR. SHURIN: I'd like to endorse that, but also to say not only is it needed in terms of expertise -- this kind of expertise needs to be brought to the table -- but it's also potentially another source of support.

For instance, we're doing a number of studies on antiplatelet agents, which have tremendous variability on a genetic basis in terms of their efficacy, and looking at some point of care testing, and bringing in the people who make the instruments so that it's part of their business plan in terms of their developing a market, is also something -- it's a problem, but in solving that problem, we may be able to get some more partners to make some of this move along. Particularly related to pharmacogenomics and the individualization of response, there are many, many opportunities here to build a research program which will exploit some of those questions as well.

So I think trying to think very broadly in terms not just of what's necessary but also what might conceivably be of benefit to somebody else would be quite helpful.

DR. BALIS: Thank you.

Dr. Curt?

DR. CURT: Yes. I'd like to pick up on Dr. Reaman's comments. The one challenge that's not

on that list is patient heterogeneity. And in clinical trial design, what you might want do is to get as homogeneous a group of patients as possible with an event rate which is meaningful as well.

Perhaps the population that would be the easiest to jump-start work in this would be children with cancer with indwelling catheters, where the event rate, according to Dr. Portman's talk, is quite high if you use the right imaging techniques, and where the children are being taken care of in a culture where clinical research is part of the standard of care, as opposed to some of the other subspecialties, where we heard that that is not necessarily the case.

DR. BALIS: Yes. I think, Greg, that that's a good point. The issue I think in using anticoagulants in children with cancer is the thrombocytopenia issue for those that are on therapy.

DR. CURT: But the other issue is that in some of the other settings, when you look at adverse events, you're not sure what's coming from the treatment and what's coming from the underlying

disease. So it gets very complex if you go into other areas as well.

DR. BALIS: Right. Yes. There's always going to be something like that, I'm sure. Yes.

Other comments? Dr. Reaman?

DR. REAMAN: But just to follow up on your concern about the thrombocytopenia, I think the prophylactic use, certainly the risk of thrombocytopenia or the presence of coexisting thrombocytopenia is a concern. But in dealing with an established thrombosis, I think you have no choice, whether patients are thrombocytopenic or not, to use some of these agents. And we really don't know which agents to use, how to use them, or how long to use them.

So I think there are still questions that could be asked even with the concern of thrombocytopenia. And you could, I think, develop a protocol so that you had specific guidelines for what you did as far as adjusting -- or not adjusting, but managing platelets and platelet transfusions in the setting of anticoagulant therapy.

DR. YOUNG: Actually, I'd like to follow up on that. That's a really good point. So this comes back to just the whole general view of clinical trials. You can design a clinical trial to be safe -- and I'm looking at the FDA mission statement, protecting and promoting public health. And if we do a clinical trial in pediatric cancer, leukemia, where there's a high event rate, and we exclude patients that have a platelet count below 50,000, or we stop the anticoagulation when patients have a platelet count below 50,000, then we're not going to learn anything about the safety in that setting.

Yet when practitioners are out there dealing with these patients, some will hold the anticoagulant. I've heard of some saying that they just cut the dose in half, based on what I have no idea. And some continue it, continue the anticoagulant, despite the thrombocytopenia. And I always do like to say that thrombocytopenia is not an anticoagulant. We have plenty of kids with thrombocytopenia that get blood clots.

So I think that's that he other part of

designing trials in a way that will be meaningful. Yes, you want to be able to answer the question. And so you don't want to be too heterogeneous. But you also don't want to exclude so many different categories so that it affects accrual. But then also, at the end of the result, you say, yes, here's what we can say about kids with cancer, but you know what? If the platelet count's less than 100,000, then all bets are off. And so then have you really accomplished something in that specific patient population?

So all these things need to be taken into consideration when designing trials. And I think that that's really a key component. I think Dr. Portman -- just as another example, right. So the EMA requested that they design a trial in a certain way. And I'll be honest with you, I was approached by the CRO or something about this trial. When I saw the synopsis, I said, there's no way this gets through my IRB. Okay?

So here's a trial that was designed in a way that it was supposed to answer certain important

questions, but then it was, at least by some IRBs, deemed to be not ethical to do the study, and they have to go back and now redesign it because it wasn't designed well the first time, and how much time has been lost.

So this clinical trial design issue is really important. And I think it's getting the right people together, not just hematology experts; laboratory experts, others who, if it's a cardiac study, are involved, and then pharmacologists as well.

It's so hard to do these studies that you've got to design it right from the get-go, so that at the end, you're going to have something meaningful and useful that'll help to protect and promote public health.

DR. BALIS: Yes, Dr. Minniti?

DR. MINNITI: Yes. I wanted to follow up on this concept that Guy is bringing up, which is the concept of trial design. But I also wanted to bring it back, depending on what the trial design is for. I mean, what's the aim?

Are we talking about a safety trial or an

efficacy trial? Because for a safety trial, I might argue that maybe you need a population that has less concomitant disease in the variables as the pediatric cancer population.

If you are looking for PK, going to frank discussion, and safety, I think you want to make sure that everything is attributable to that drug that you are studying. If you are looking for efficacy, that's a different type of trial. So I really think it depends what we are looking for in these initial trials.

What's the first trial? Is the first trial going to be an efficacy trial, or it's going to be a safety? You know, it's a phase 1 or a phase 3, I guess I am asking, and then I will choose the population accordingly to the question that I am asking.

DR. BALIS: Yes, Dr. Aly?

DR. ALY: I think one of the issues, at least for the neonates, is the amount of blood that will need to be withdrawn from the baby. So it's almost impossible to really have a good study in neonates or

preterm infants who have central line and thrombosis that we're required to withdraw 5 cc of blood when the total amount of blood of this baby is only 50 cc or 60 cc.

So I believe, having like an accurate point of care at the bedside that we rely on in monitoring the safety or efficacy of these drugs will be definitely a prerequisite for any enrollment, at least in the neonates.

The other point I want to point at is having awareness. When we have a certain registry already existing, such as the ELSO registry for ECMO patients, for example, we can just make sure to really include in these data for all ECMO patients nationwide, adding certain points of data about thromboembolic problems, and what kind of drugs was used, and what are the complication. You will end up having, by the end of a few years, a huge population with thromboembolic diseases and already treated that we can get analysis, and this data can give us good help.

DR. BALIS: The other issue, I think, since

we're talking about neonates, that I was going to raise, that wasn't on this list, is the issue of pediatric formulation. I assume that that would -- unless it's an IV drug, it is going to be limiting to you to do these studies earlier, assuming that that's not a high priority for the company to develop.

Have you done any studies with oral agents in neonates at this point?

DR. ALY: We did not. And I'm not aware of, really, that many studies done on oral anticoagulant for neonates. I'm not aware of. The only thing we use frequently is indomethacin and ibuprofen for different indication. That's the only thing I could think of.

DR. BALIS: Where it's a side effect?

DR. ALY: A side effect, yes.

DR. YOUNG: The issue about different formulations is definitely important in pediatrics. And this is another area where I have to commend industry, who's done a lot of work.

I know both for apixaban, as we heard, and

I know for rivaroxaban, also, the company's created a palatable -- I got to taste the rivaroxaban; it's not orange, but it didn't taste bad -- oral formulation that kids will actually be able to take that's a liquid that you can potentially put down an NG tube. Now it's fascinating to hear that the -- the NG tube recovery study I thought was very interesting.

But the thing we have to remember, though, too, is that in anybody who has or had young children, sometimes trying to get them to take anything orally is you hold them down and pinch their nose and shove it down their throat, basically. But parenteral formulations that are subcutaneous, and while they are somewhat painful, it's amazing to me that the kids pretty well get used to it, and the parents learn to give it. And in some respects -- and depending on the drug, of course, and its bioavailability, sometimes that actually is a more reliable way of getting the drug in.

So there's been a huge push towards oral anticoagulants in adults, and then clearly there's lots of reasons why. And I think that that's a good

thing to help for many children as well, and getting a liquid formulation is important. But I think, at least in pediatrics, there's always going to be a role for a longer-acting parenteral agent because sometimes it's just too hard to use the oral route.

DR. BALIS: Dr. Minniti?

DR. MINNITI: I cannot resist telling you this. In thalassemia, actually, they did a study regarding the -- for iron chelation, now we have an oral chelator instead of the subcutaneous test. And there was a small study, and it talked about parental stress in giving medications. And it was exactly like Guy said. The stress over giving the oral extract was so much that most parents -- this was in Europe -- requested the subcutaneous formulation because they said the family life was so much better, apart from the compliance. So you are right.

DR. BALIS: Just to get back also to the accrual issue -- because I think it does start with that; if you can't get patients on the study, nothing else really matters -- my impression from what I heard at this discussion was that a lot of the

restrictions are not coming from the investigators. They're coming from the regulatory agencies or from the sponsor. And I think that does reinforce the issue of making sure that the investigator is intimately involved in the design of the trial where those decisions are made, because, oftentimes, if you're handed a study that's already been written, particularly if it includes a lot of restrictions on eligibility -- which are often put there for conceived reasons of safety -- the trial may be undoable at that point.

That's the one thing, I think, of this list of things that's probably the easiest to overcome or control, as far as I can see, of the things that we have.

Dr. Kaskel?

DR. KASKEL: So there are certain focus groups, advocacy groups, that work like with the Office of Rare Disease, representing the different conditions. And parents come to the table. And one discussion came out of a meeting last year at the Office of Rare Disease about bringing them to the

table earlier in the development of a study, whether it's a registry by a repository or a clinical trial. So you could, once you pick your rare disorders, bring in representatives of those groups to meet, and they can disseminate information to their networks about the trial. And you probably -- I mean, I don't have the data. I suspect you'll have better recruitment.

DR. BALIS: Dr. Shurin?

DR. SHURIN: That's actually a terrific approach. The adults with congenital heart disease group has become extremely active. We were able -- actually, when Dr. DiMichele gave her presentation, she talked about one of our Marfan studies.

We were able to get the Marfan study done unbelievably efficiently because the Marfan Foundation went out and recruited patients for us on their website. They said, don't go on a certain off-label. Enroll in the study. Help us answer the question. And we actually concluded accrual in this very rare disease early.

My guess is with things like people who are survivors or parents of survivors of congenital heart disease, enrolling patients in a study which they think is important will be easy. And they're our best advocates, no question about it. And my guess is the same thing is probably true in the nursery.

DR. BALIS: Dr. Freedman?

DR. FREEDMAN: In Dr. Young's presentation, I think you emphasized the value of interacting with the FDA to be able to achieve some objectives of your research. And I think the basic issue that we're discussing here is the incomplete labeling information that we have for a drug that is widely used and that is very important for the pediatric population. And, certainly, the NIH does very good work in supporting basic research, and to some degree applied research. But the point is that research projects, they are at the mercy of the study sections.

On the other hand, when you're dealing with a situation like this where you need certain specific studies to be done to reach certain objectives, it

seems like you need something else to drive the issue.

I get back to my question earlier as to what FDA actually has at its disposal in order to facilitate getting answers to the questions that brought us here today in terms of interaction with NIH, in terms of interaction internationally.

What is it that can be done from your end, realizing that you're also the regulatory agency? So you may have a conflict when it comes to participating in the research.

DR. FARRELL: Right. Well, I think the smartest drug development is always when the principal investigators or the co-principal investigators are in the room with the pharmaceutical company to actually work with the FDA to negotiate issues around the trials. And often, we are having a meeting with just the pharmaceutical industry, or maybe we'll have a meeting and the cooperative group will show up.

But since we're all partners here, unless we're all at the table understanding each other's

opinions -- I think the FDA could send out a "You need to do this," and not understanding, because maybe the scientific person isn't in the room, the logistics of actually this request and why it might not be feasible. So I think everybody needs to be in the room at the time the negotiations for these types of trials are going on, and I think that'll facilitate a whole lot.

DR. FREEDMAN: In terms of approval, you mentioned international coordination, I think, earlier.

DR. FARRELL: Right. We had hoped to have the EMA participate in this conference, but they're actually closed yesterday and today. And they're going to be looking at the webcast from this meeting tomorrow, and we'll be following up with a meeting with them to discuss pathways forward.

DR. FREEDMAN: And my last question relates to the NIH. To what degree is FDA permitted or allowed to interact with the NIH with regard to setting program objectives for drug studies?

DR. FARRELL: We can interact with NIH and

NHLBI. Sometimes when it comes down to a specific product, sometimes our sister agency has to go through clearance to make sure there's no conflict of interest. It's not usually an issue, but, yes, we can partner across the table.

DR. BALIS: Yes, Dr. Durmowicz?

DR. DURMOWICZ: I think also, through this off-patent BPCA process that we've spoken about a little bit before, is we do have a way of working with NIH, actually, through NICHD. And, actually, NICHD is mandated to develop a list of needs in pediatric therapeutics and a research agenda to address those needs, so that we are a consultant in that process to NICHD.

DR. YOUNG: And I think I could add also that on orphan product drugs, which I know you're not necessarily part of, they do have a granting mechanism to do studies in orphan diseases. And pediatric thrombosis, regardless of how much the incidence has risen in the last 10 years, is still definitely an orphan disease, as defined by the federal government.

So that's another way that FDA -- not necessarily the people sitting here at this table -- can help, but another way to try to get studies done as well. So that was a very useful thing for me. I mean, we had a study. It's published. And it's only the first step for that particular drug; there has to be other steps to follow. But I think that's another collaborative way.

I completely agree with your comment. I think I've come to the FDA twice before as a sort of consultant with some of the drug companies, and those were always really, really fruitful discussions because then you have all parties at the table. So I mostly sat silently, but then there was a question, and then the drug company representative said, okay, Dr. Young, can you answer that one? Because I wasn't there speaking on behalf of the company. I was just there to answer questions if they came up.

But that was very fruitful, and it led to basically an acceptance of the development program for that specific drug. So I completely agree,

having all the people at the table really helps because, otherwise, it's a two-legged stool.

DR. BALIS: Dr. Kaskel?

DR. KASKEL: Right. To go along with that, the BPCA, they have a meeting in December, first week of December. And there's a hematology working group among the kidney group. So this is a perfect time for them to bring this up for prioritization.

DR. DURMOWICZ: Exactly. And Dr. Neville or Dr. Snyder may want to speak more to that. But these issues are being also discussed in that format, too.

DR. NEVILLE: And I would just add that I think the PTN so far is a successful model of how NIH and FDA can work together and partner with academics and potentially industry. Quite a few trials are going forward, the working groups. In my estimation, the phone calls have been quite successful. So I think it's a good model.

DR. DURMOWICZ: The working group is trying to identify some of the priority products to evaluate, and, again, what are the gaps in actually evaluating those, such as endpoints, trial design,

and other things that we're discussing today here a little bit as well.

Note that enoxaparin, that we've spoken about quite a bit, is something that we have nominated in the past for study under NIH, and this will be discussed by the working group and hopefully will come with some recommendations.

I might have one additional thing to add, along with discussions with EMA.

DR. BALIS: Sure.

DR. DURMOWICZ: The pediatric group does discuss with EMA on a monthly basis products just for the venue or format, so to speak, or a framework for sharing information built on scientific discussions, ethical issues. And sometimes we'll discuss specific products or specific conditions or classes of drugs.

So that's another forum that we can use to continue discussions on an ongoing basis.

DR. BALIS: Thank you.

Dr. Shurin?

DR. SHURIN: Yes. In terms of the back and forth among FDA, NIH, and industry, I'd say there's a

ton of it at the moment. I'm going to be spending the next two days at a target validation meeting that the senior leadership at NIH is having with industry, looking at mining genomic data, primarily.

Dr. Farrell and I have a lot of -- and Dr. Robie Suh and I have a lot of collaboration. We've had workshops to identify targets that are meaningful from a scientific standpoint that the FDA can also use for drug approval. Those have been very helpful conversations for us.

We don't necessarily influence each other's agendas exactly, except that these conversations are incredibly helpful for us. And it's been terrifically useful I think for each of us to understand where the other is coming from.

I co-chair with Dr. Woodcock a subcommittee of the NIH-FDA Leadership Council, which is focused on clinical studies and clinical trials to try to set up some mechanisms to improve the communication. But most of it is very much at the level of the people who are actively involved in approving the drugs and designing the studies.

DR. BALIS: Okay. I think we all pretty much agree that these four factors in some way or another do represent real challenges to moving these studies forward. And we've gotten a little bit into the second question in the discussion, so why don't we move on to that. And that is to discuss whether creation of a national or international consortium could facilitate the enrollment to pediatric studies, as well as pathways to creation of a consortium.

So we actually had a fair amount of discussion about this this morning, and I think part of it related to the infrastructure-type funding. And so I guess the bottom line from that was that, to be practical, we had to come up with different ways, more creative ways, if we're going to form some type of consortium or group using the existing infrastructure to do that.

Dr. Shurin, do you want to make any additional comments about where we might move? And I should frame this to say you'll see when we get to question 2, we're going to be talking about specifics of conditions in drugs, et cetera, that we're going

to be studying. So we haven't talked about that yet, but I think that's going to -- because of the fact if we're working on an existing framework, that's really going to be where we hang this. So we in some ways are doing this backwards, but I think --

DR. SHURIN: It's okay. I think that, first of all, the infrastructure is absolutely essential. It's really impossible to do the work if you don't have the infrastructure. The problem is, we have to make the investment in infrastructure when we've got two things in place. One is a scientific agenda, and the other is the scientific and investigator leadership.

If both of those exist, then an investment in the infrastructure pays off in spades. I would say that the Pediatric Heart Network that we support is a tremendous example of that. It's incredibly valuable. And we've done studies there that we never would have been able to do if we were setting up individual studies by bringing people, different disciplines, different -- so we've got geneticists and surgeons and cardiologists and radiologists all

across the board.

But making the investment in the infrastructure without having either the scientific priorities identified or the investigators who are really going to lead it doesn't work, and it ends up not being very productive.

So I think the key issue is you need -- I think that sort of the answer is E, all of the above. But I think that the issues of the scientific priorities and the investigators really come first. And then as far as we're concerned, it's a very, very worthwhile investment.

DR. BALIS: So how do you think that gets started? Who is going to -- we obviously have some leaders here, but how do we identify who they are, and, at least as a starting point, getting them together just to discuss what the scientific priorities are?

I mean, we're going to do that today, but it clearly needs to be a much larger group of people, and those invested in doing the trials that are involved in that.

Is that something that your institute --

DR. SHURIN: That actually is something that my institute does a lot. In fact, I just sent to Dr. DiMichele a strategic plan for pediatric pulmonary research, which our lung division did about two years ago, a very similar kind of issue, because the issues are so -- it's diverse. It's not like it's all going to be the same group of investigators. It's not going to be the same solution for all of these.

But what we can do is to try to get people together to try to work on the science and get people enthused about the collaborations. Often one of the most helpful things is getting people together who don't actually know each other already, because what we often find is that -- and I think this is really true here; it's not only the laboratory medicine, but people from a whole bunch of different places -- when people sort of come together and understand that they're all addressing many of the same kinds of issues and that together they may be actually able to solve some of them, people tend to get very

enthusiastic about it.

So we certainly can do that. We would never actually hold anything like that without having FDA at the table. So we certainly can do that. But I would just remind people that the pediatric oncology cooperative groups were actually investigator-initiated at the very beginning. So what happens is you get some infrastructure that brings people together. But that was actually created by a lead group, core group, of people who came together with the problems that they wanted to solve.

DR. BALIS: Yes, Dr. Young? Dr. Young, I'm sorry. Yes, it was you.

DR. YOUNG: Okay. Sorry. I thought you were going to someone else. Sorry about that.

So that's very interesting. And let me give an example of something that has just gotten going, and maybe that could serve as a model, although it has just gotten started, so it can't really be a full model, but maybe you could start following it.

So the NIH recently got together a multidisciplinary group of experts, included

FDA -- Susan knows; Donna DiMichele actually put the group together -- to look at some of the laboratory monitoring tests in hemophilia.

Now, the topic is not important. The fact is that it was an international group of experts that got together. There were representatives from NIH, FDA. I think CDC was there as well. There was presentations on the area, and then there was a discussion about how to move forward. And I think the interesting thing that came out of that is that -- oh, and industry was there, too. Let me not forget. There was multiple representatives from various drug companies.

What's happened so far is that the decision was -- obviously, funding was required to move this forward. Right? Without money, there's no mission. And industry was interested in moving this agenda forward because the specific topic was of interest to them.

So what's happening, actually, is that through, actually, not NIH but NIH Foundation, we've met with industry to put some pot of money into the

NIH Foundation. And then the group -- and the group has -- it's an international group. There's now leadership. There are subcommittees, so it's pretty well organized. The group then leveraged that funding in the NIH Foundation that is put forth towards this mission to answer the basic question, just as we have here, to move things forward.

So that might be an interesting model to consider moving forward, to get the right group of people together and to get some funding behind it so that then the mission can go forward.

DR. BALIS: It seems like the other groups that may need to be there, if you're eventually going to be using them, are representatives from the existing groups that you want to try to work with -- the Children's Oncology Group, the Heart Network, and the rest. Because you're going to have to get them engaged at some point if these studies are going to be done.

The other thing that we've done in oncology, or that's happened, I think, partly in need -- I think Susan's right that most of these groups

initially formed 50 years ago, whenever it was, around investigators and the scientific part, and then the rest fell in place. But there have been little spinoffs. So there are consortia now that are very much more specific in terms of what they do. There's a phase 1 consortium that just does early-stage-based clinical trials. There's a brain tumor consortium, and to some extent, especially the phase 1 consortium, still utilize the resources of the big group, the cooperative group. So they use the same data system in terms of entering their data.

So there may be other models that you can look at in the way that the cooperative groups work that may be useful for setting up smaller interest groups of people that are clearly focused on enrolling patients and doing these clinical trials.

I think you've got, Dr. Young, a good start on that, since you've already, at least in some ways, identified some of the places that you think are more likely to enroll than others, just from practical experience.

Other comments?

Greg, do you want to make any comment about -- I know you don't run the Children's Oncology Group any more, but the potential for using that as a way to get some of these studies done?

DR. REAMAN: Well, I think within the context --

DR. BALIS: Cancer-related. Let's say cancer-related.

DR. REAMAN: I think it's something that, for the last several years, there have been discussions about potential cancer control studies, looking at prophylactic use of anticoagulants to prevent central venous catheter-related thromboses.

So I think -- yes. So I think in the setting of thromboembolic complications in the cancer population, I think the COG would be an appropriate place to do these kinds of studies. Leveraging the COG infrastructure to do non-cancer-related studies I think would probably be more difficult. It may be that the organization itself would buy into it. But, again, these are resources that are predominately federally supplied, and there is some control, if you

will, oversight approval, of how those resources are used.

So to just say that we're going to use the data management system and the clinical trials management system of the COG to do coagulation studies or anticoagulation studies in a non-cancer population I think probably wouldn't work. But I do think that interested hematologists, interested laboratory medicine people, could certainly work with the Cancer Control Committee of COG to put together at least a starting, or at least as a start, a prophylactic study in kids with central lines.

DR. BALIS: Do you think the leadership of the study, the study chair, would be best coming from somebody who's an oncologist or somebody who's primarily --

DR. REAMAN: Personally, I think we've introduced the concept of actually having co-chairs of studies. So I think the oncologist is aware of the complication. The hematologist might be a little bit more aware of the therapeutic intervention that should be evaluated.

So a team approach. The only way we've gotten anywhere with the cooperative groups is through the concept of team science. I think team science should begin with the initiation of a study design. So whether it's run by an oncologist or a hematologist, I think both could do it. Both should do it.

Actually, there is precedent for that. There are cancer control studies that are chaired by infectious disease people or by nutrition specialists and not oncologists. So I would say it's an opportunity that ought to be explored. And I think it's an opportunity that could be greatly enhanced and facilitated if there were to be some industry support as well because these studies have a well-recognized reputation for not having a great deal of interest at the institutional level because they're sort of over-stretched and resource-restricted. So if there are additional resources that are made available so that these studies can in fact be opened at participating institutions, patients can be accrued, and studies accomplished.

DR. BALIS: I think what Dr. Reaman is referring to in more concrete terms is that enrollment on these cancer control studies provides -- we get a per-case reimbursement for enrolling patients on clinical trials, and it provides additional per-case reimbursement to the institution. So there's actually money that comes in from enrollment.

Oftentimes, although this may not be the case, the cancer control studies are very short-term studies. They're done over a very specific period of time compared to our cancer studies, which require years of follow up. So there can be a significant incentive to enroll the patients, if that's the case.

What about another subspecialist? Can we see a similar path forward to working with other groups that are existing in order to get these trials up and going, looking at the subpopulations?

Dr. Artman, can you comment about cardiology?

DR. ARTMAN: Yes. And, again, I think relying on the Pediatric Heart Network would be the way to go. They have a steering committee that vets

all of the protocols, and I would think the leadership from one of those groups, from that group, would be ideally positioned to integrate more collaboratively with these other already in existence structures, organizations.

DR. BALIS: And interest, do you think it's there as well?

DR. ARTMAN: Oh, I think so, yes. Yes, absolutely. And, again, especially around those Fontan patients. The very first trial or study -- it wasn't even a -- well, I guess it was a study -- of the Pediatric Heart Network when it first formed 10 years ago was a cross-sectional study of Fontan patients, and just the characteristics, the clinical characteristics of that group. And then, subsequently, there's been a number of spinoff studies from that original group. So I think they'd be very interested in a thrombosis anticoagulation study in that group.

DR. BALIS: So it seems like -- to go to the question -- there are at least two groups and two very specific questions that could be addressed

without a lot of extra resource or infrastructure in place, meaning the issue of thrombosis in catheters in cancer patients, and then these issue in these Fontan patients with the use of anticoagulants, that at least as a pilot would maybe be the way to start to put these cooperative groups or consortia in place.

Dr. Shurin?

DR. SHURIN: And we actually have a couple of studies going in conjunction with NICHD using their networks, their transfusion studies. So basically we're funding -- it's their network, their organization for it.

It doesn't actually decrease our costs, but we have a much greater level of confidence that we'll actually be able to accrue the patients because we're dealing with a group of investigators that has a track record of doing these studies.

We wouldn't do that if we didn't have a very strong expression of interest from the neonatologists and the pediatric folks, because unless they're committed to it, as you well know, it won't happen.

DR. BALIS: Go ahead, Dr. Reaman.

DR. REAMAN: I think in addition to what you suggested, Dr. Balis, as far as these being pilots, I think it also presents an opportunity to bring interested investigators together. And I think that's probably even more important than the proof of principle that a pilot study might have. But bringing the people who really have the interest, the passion, together to continue to design studies and other indications and other populations, I think that would probably be the number one benefit from actually starting these kinds of studies within infrastructures and networks.

DR. BALIS: Dr. Sekeres?

DR. SEKERES: So I'll play the role of naysayer. So what I've heard is going back to relying on the Children's Oncology Group as an existing network to conduct at least one of these studies, is given that we've all acknowledged that participation in these cooperative groups is more or less a labor of love -- institutions actually lose money on them -- is that a viable answer? Is that

going to incentivize people to enroll patients onto these studies?

DR. REAMAN: No, it's not. And, in fact, patients don't get enrolled on these studies because there is no incentive, which is why I made the statement that this is an opportunity to have industry get involved because industry can provide additional support.

So the Children's Oncology Group has a number of industry-sponsored, industry-supported, co-supported, co-sponsored studies for which there is additional per-case reimbursement. And in some cases, the additional per-case reimbursement is really quite handsome and could, should, serve as an incentive for accruing patients on study.

So I think there's an opportunity here. But you're absolutely right. Just adding more studies to a system that's already stretched with just federal support isn't a satisfactory alternative here. But there is an opportunity, and a very real opportunity, for supplemental support with industry sponsorship.

DR. SEKERES: So, again, I'll play the role

of naysayer just because I'd like to hear this kind of fleshed out a little bit more.

So within the adult cooperative groups, we also have these industry and cooperative group partnerships, which I think are -- we basically couldn't function without them. And industry will provide monies to a cooperative group, either for help with the conduct of the study, which is less common, but more common is to provide drug through CTEP.

I still have to doubt that the amount that would be negotiated -- I'm assuming that industry would negotiate with the cooperative group, come up with a dollar amount that they would reimburse each institution for a patient, that there still would be some institutions that would lose money on that.

DR. REAMAN: It's always possible. But I can tell you that our experience, at least in the past, has been to negotiate with the understanding that we know what it costs institutions, sort of a cross-section of institutions who are members of the cooperative group, what it costs them to do clinical

trials, specific clinical trials, and what might be required as far as enrollment of patients, treatment of patients, obtaining biospecimens, storing biospecimens, processing biospecimens, collecting data, submitting data.

So that's all been figured into what we have negotiated in the past with industry for supplemental support. And in every one of those situations, the amount of supplement exceeds by a thousand percent what is given to the cooperative group from the NCI for per-case reimbursement.

So it does cover. But, as you mentioned before, you do all of the work, and then you get the remuneration for the work that you've done. It's not a very good business model, but, unfortunately, it's the model that exists in clinical research.

DR. BALIS: Dr. Neville?

DR. NEVILLE: Well, if I could echo what Dr. Balis said earlier, I think in some ways pediatrics is a different world because we've never gotten paid for any of the studies we've done, so we've gotten very good at using multiple resources to

fund those studies, like industry, like cooperative groups, like philanthropy.

I think, too, you can't underestimate the power of academic currency. Right? So even if something is a money-loser for an institution, the prestige of the publications or membership in whatever cooperative group pays for something.

DR. BALIS: Dr. Shearer?

DR. SHEARER: Another advantage of using the established mechanism of Children's Oncology Group is this is a known vehicle for those of us in pediatric hematology/oncology, and it would therefore serve effectively to broaden the net.

If we broaden the net of potentially interested investigators, we will subsequently broaden the net of potentially interested subjects, and therefore address the issues that we've talked about already in terms of inadequate accrual and coordination of subspecialists.

The second point there, coordination of subspecialists, spins off the role of pediatric hematology/oncology because, as we've heard today

already, most of the subspecialists prescribe anticoagulation upon recommendation of the hematologist in consultation.

So the argument is that if you get more interested pediatric hematologists/oncologists, which you will definitely do through Children's Oncology Group because that's our established venue, you will then serve to meet the goal of increased accrual and greater subspecialty participation.

The second thing that I'd like to echo that's already been said today is that this is not a one-size-fits-all research design. There will be some institutions who will be well-suited to study thrombosis in certain populations with certain drugs, and others that are suited to study other anticoagulants.

So I think that as these plans go forward, we can look at it that way. We do need at least a loose infrastructure, but I think that this is going to be an individually specific enterprise. The funding is going to be very different. I think that we're all going to be relying on more support from industry as

that becomes available. Not all people will have the advantage of grant support. But I think by casting a wide net within established vehicles for pediatric hematology participation, we'll meet the goals that we've talked about today. So I think that's important.

DR. BALIS: Thank you.

Dr. Sekeres?

DR. SEKERES: Rebuttal.

[Laughter.]

DR. SEKERES: Sorry. To reply to Dr. Neville, I totally get it. Right? There is obviously academic prestige in participating in a cooperative group. There are also a lot of politics in authorship with cooperative groups.

I think the business model of losing money on trials, relying on philanthropy, is something that you as pediatric oncologists can change. And you have a bargaining chip now. Companies have to do studies in kids to get drug approval. Right? You've heard this from the FDA. And there are a limited number of kids in whom they can do studies.

So I don't think that should be an accepted model any more. I think there should be a way to actually break even in doing studies, and shouldn't have to rely on philanthropy to do these sorts of studies.

My second response is -- and I see this playing out all the time at my institution. If there's a study we can participate in where it's some novel targeted therapeutic for an oncologic indication versus an anticoagulation study for catheter-related thrombosis, what do you think most investigators are going to choose? Right? It's not as sexy to do the thrombosis associated with the catheter study.

So maybe one approach using the Children's Oncology Group -- and I do think that is the best mechanism within the U.S.; it's there; everyone's already playing together -- is to add that onto an existing study. It makes it more challenging in doing that, but if you combine it with a study where you're looking at a novel therapeutic, I think you're going to get a lot more people who are going to do

it.

DR. BALIS: Yes. I think we've done that both ways.

The other point I'd make, which I think is more true in pediatrics than adult, at least in cancer, is that we have such a limited patient resource, patients that we can enroll on trials, that we try to learn the most from them. And so I think we're also used to putting patients on many studies.

I mean, the one complaint that I get is that when you walk in to see a family of a patient going on study, that you walk in the room with seven consent forms because there's so many different things that we want to try to enroll the patients on to try to get the most out. Where that creates an advantage for what you're talking about with resources is that if somebody's already on a leukemia study, there's a whole lot of data stored on that patient already from that trial that you don't need to reenter. And so you can more efficiently do it. There's a lot less information you have to gather that's just study-specific for that study. It makes

it, I think, easier to do it for that reason.

Dr. Neville?

DR. NEVILLE: If I could just say, so my point wasn't necessarily being revenue-negative or relying on philanthropy as much as being creative. And one thing I want to bring up is there are many other populations besides just cancer. So I think that Children's Oncology Group is one thing, but now there's a Neonatal Network. Now there's PTN. So I think we're much more facile than we were 10 years ago.

To your point, at our place, our clinical trials unit is doing both studies. So we are doing early phase drug development in oncology, and we're doing catheter-related clots. So I don't think they have to be mutually exclusive. And I agree with Dr. Balis that because, historically, any of the diseases that we've studied are small populations, not to say there's not politics, but I think we have much more of a common goal of gleaning as much from each patient.

DR. BALIS: Yes, Dr. Kaskel?

DR. KASKEL: Because I'm the sole pediatric nephrologist on the committee, I just want to remind you that there is another rare consortium, and that's pediatric nephrology end-stage renal disease in children. Several thousand in the United States; every year there's 2 [200] to 300, at least, acute emergency dialysis treatments in pediatrics which require a catheter, and many of those have catheter problems related with thromboembolism.

We have three networks that are very active across the country, one called NAPRTCS, one called NIDDK, and an NICHD-funded study called CKID, which has enrolled most of the chronic kidney disease children in the country; and then a support group called NephCure, which is a focus group on nephrotic syndrome.

So there's three existing networks, probably another one I missed, and the organization, American Society of Pediatric Nephrology, which would partner with any initiative here.

DR. BALIS: That's great. So it sounds like we have lots of options there.

Let's move on to the third part of this question, and that's to discuss whether development of standardized template protocols could facilitate the initiation and conduct of pediatric studies of anticoagulants. In our discussion, we are to provide suggestions for indications for which may be candidates for standardized protocols, potential study designs, and whether global use might be feasible.

Yes, Dr. Young?

DR. YOUNG: I can start with that. So there is an organization called the -- you've heard before today -- the International Society on Thrombosis and Hemostasis. And that society has, as a sort of branch, something called the Scientific and Standardization Committee, SSC. And one of the papers from the pediatric SSC was demonstrated there, which was about what are the outcome measures that should be looked at in pediatric anticoagulant studies.

Another paper that, actually, I'm working on with one of those other authors is basically trying

to develop this template, in fact, is trying to write something that would be an essentially scaffold or model by which a new anticoagulant -- so we're not talking now about enoxaparin and things like that, but the new anticoagulants, a model for how they should be staged and studied.

So we heard, do you start with a phase 3 or do you start with a PK or a safety? And so the goal of this consensus paper recommendation, if you will, is to provide fairly general -- nothing specific, but fairly general guidance about how you would approach taking a new anticoagulant from what you know in adult studies, and then taking it through the stages of development such that you have as much as you can say, given the challenges that we've all discussed today, about safety, about safety dosing and efficacy.

So that's something that I'm in the middle of working on. And I think that there will be some kind of template that comes out with respect to that.

In terms of standardized protocol, potential study designs, I think that's a bit harder to do

because I think that we've heard -- so we have pediatric nephrology, dialysis catheters that need perhaps prophylaxis. We've heard about Fontans, a completely different situation from pediatric dialysis catheters, where there's abnormal flow and needing anticoagulants. And then there's just the run-of-the-mill, I'll call it, even though it's not common, venous thromboembolism that happens in kids.

So they're really rather unique settings. And so I think to try to really standardize something across these settings would be difficult in terms of suggesting a trial design for this or for that.

But I think an overall template; okay, here's a new drug. This is what you need to do first. Get some PK data or get some animal data. Get some toxicology. Get some PK. Get some safety. Then the second stage. Then the third stage. We've seen, from Dr. Portman's presentation, how some of the drug companies are following that. And they're somewhat variable, but there is a common theme there, single-dose PK or multiple-dose PK, followed by more elaborate trials after that.

So I think, generally speaking, yes, we can come up with templates. I think that it's then incumbent upon investigators to then take that template and then look at the different patient populations and decide, hey, this is a good one. This is a good drug that we should look at in preventing clots in nephrology catheters. This is a good one for Fontans, or just investigators have to say, well, I like this drug and I think it would be great for Fontans, and I'm going to approach the Pediatric Heart Network to do a study; or, I think this might work for pediatric cancer, and approach.

So those are some of my comments on that.

DR. BALIS: I know that Greg could speak to this as well as I. But at least in the Children's Oncology Group, there's a -- when I say "format," standard format in terms of the way the protocols are written so that users always know what section to go to, to look up whatever they need to know about the study.

The next level in terms of this is -- what you mentioned is outcomes, having very specific,

well-discussed, objective measures of the outcomes that you want to measure. And that may not be so disease-specific, and those might be important.

So in cancer, we have CTEP's common toxicity criteria that everybody uses to semi-quantify the severity of toxicity, or we've got RECIST criteria that we use to describe how a tumor respond to therapy.

So there are clearly advantages to having that and using them universally so that everybody understands. The one thing that I think that you have to be careful about in being too standardized is stifling science. If people feel like they have to fit into a mold, they may be less interested or we may not get the best study out.

One of the disadvantages, for example, of all the criteria that we've developed, the common toxicity criteria and the RECIST criteria, is that they categorize things. And when you categorize, you lose information. It means you have to do larger studies because you're not using a continuous measure of outcome.

So there are tradeoffs with this, and I think if you're going to do this, you should learn from what the other groups have done in doing it and try to pick the best in terms of what's worked the best.

Yes, Dr. Neville?

DR. NEVILLE: I actually have a question for Dr. Young. So one of the things we're struggling with, with BPCA, is what would you suggest for a study of the older drugs? I think with FDA involvement and EMA involvement, maybe it's a little easier bringing drugs forward. But we're sort of left in this position of enoxaparin's used all the time. Warfarin is used all the time. Yet, the studies supporting their use aren't there.

Do you have any suggestions?

DR. YOUNG: Well, I think that particularly with the enoxaparin story, and that's why I put that up there in my slide, as a cautionary tale -- so the suggestions are that -- I'm hearing some good ideas here at the table. So one thing is for investigators like myself, who think, hey, this is an important issue, to put together a grant application as I have,

and hopefully that gets funded. It may or may not. If it doesn't, though, there's no point in giving up on the idea. But from everything I'm hearing from Greg, I think bone mineral density has been a concern in pediatric oncology, be it with the steroids in leukemia and other drugs that are used.

So that might be an area where there's some common interest, saying, look, there are concerns for bone mineral density in pediatric oncology. There's concerns in anticoagulation. We know that cancer patients get clots, and maybe there's a way to dovetail and kind of work together there. So that would be another outlet or avenue for approaching it.

Hearing about nephrology, it's another area. I didn't realize that patients get that much heparin on a regular basis, because of all the drugs that cause bone issues, unfractionated heparin is actually the worst offender of all of them.

So it sounds like there are some opportunities, either -- and, again, opportunities have to get funded. So either it's an NIH-funded or other funding mechanisms, or working within COG to

try to work on that.

So I think that that's where we'd have to go with the older drugs, is to find mechanisms of funding for those sorts of things, orphan product drugs perhaps as well, and philanthropy perhaps as well.

Unfortunately, Dennis Quaid was never interested in supporting any of my research, by the way. I'll throw that out there. So in return, I don't go to his movies any more.

[Laughter.]

DR. YOUNG: But there are, I think, ways to try and approach those, but you need to have interested investigators.

DR. NEVILLE: Well, and one of my concerns is the efficacy endpoint because we don't really even truly know the incidence of clots. Right? And imaging is quite expensive, so who's going to sponsor that?

So then I guess my question isn't as much about organizing a trial as what do you measure? I mean, what do we measure to compare new agents

against enoxaparin or warfarin? And can you get the cardiologists to consider doing something other than what they've been doing for years and years, or the hematologists?

DR. YOUNG: Yes. So along with the issues I mentioned about bone mineral density, trials like this, if you're going to design them, and as to what Dr. Balis said, you want to answer as many questions as you can. So in this grant application, I didn't just throw out the bleeding and the clotting: Yes, we're going to follow that up as well, and look at post-thrombotic syndrome, and try to answer as many questions as possible within this type of trial. I think the design of looking at bone mineral density is one way to get around powering the study, okay, because we think that there's going to be a difference there. So you can power a study with that as a primary endpoint.

Powering studies for efficacy in pediatrics is impossible. You'd need thousands of patients, and those trials I don't think are every going to get done. I believe that there are some that are being

proposed through these new oral anticoagulants, but frankly, I don't know that those are going to get completed, in my opinion.

So it's a matter of, as we've heard multiple times today, leveraging what's out there. We have COG. We have other mechanisms, and then trying to work together. And then clinical trial design is the other thing we discussed, about endpoints.

In terms of radiology, in pediatric hematology, we do recognize that post-thrombotic syndrome is an issue. We do recognize that recurrent thrombosis is an issue. There's a pretty decent amount of data on that. So, for example, with some of the trials we do, it's building as much into the trial that's actually standard of care. So in my institution, we get an ultrasound or a follow-up imaging study a month after the clot, three months, six months, a year. That's our standard of care because we think it's important to do that.

Now, if you're going to design a trial, you can say, well, look, that's standard of care. I don't have to pay for that. That's already going to

get paid for anyway, whether the patient's on the trial or not. And so leveraging some of the standard of care stuff within your trial, and then using the funding to support the infrastructure and then answer specific questions like a bone mineral density, that's not standard of care, so that would have to get paid for.

That's the kind of innovative design, and that's why we keep coming back to trial design, that you can do to answer multiple questions at the same time with as few resources as necessary and as little funding as necessary.

Hopefully that answers some of your questions.

DR. NEVILLE: No. That's a fabulous answer, and, actually, another lesson from oncology. Right? How many things on the COG trials are standard of care?

DR. BALIS: Oh, everything. Yes.

DR. NEVILLE: Yes.

DR. BALIS: Dr. Curt?

DR. CURT: Back to the issue of standardized

protocol. You might not want to have a standardized protocol per se, but maybe your standardized protocol section's relevant to clinical trials in general but pediatric trials specifically, like background formulation, juvenile tox, PD, PK, biomarkers and study endpoints, and whatever else makes sense, so that people would have a framework of what would need to be in the protocol without, as you say, stifling scientific creativity.

DR. BALIS: Dr. Shurin?

DR. SHURIN: This is coming back to that last question about the endpoints. I would be stunned if anybody knows the bone density of a normal population of 2-year-olds. So again, you think about who we need to have at the table, but we certainly need to have the people who know those kinds of things engaged in this.

NIAMS is one of the institutes at NIH -- musculoskeletal, arthritis, dermatology, skin, that's what the S is -- and NIBIB, which is bioengineering and imaging, would both be potential partners in this. And potentially, you could

actually get, again, support from industry to people who make these machines. Okay? Again, as they see these kinds of things as potential markets, they might well buy into this.

But my guess is one of the difficulties of looking at imaging to measure this is we don't actually know what normal is. You're going to be comparing a study with a person being their own control, which may not be adequate.

DR. BALIS: Dr. Minniti, do you have a comment?

DR. MINNITI: This is a very important conversation and everything, but I'm going to be a bit of a naysayer like Dr. Sekeres. I am concerned into piggybacking protocols into COG like bone density, let's say. Well, they already get bone density problems from the Decadron that they're using in ALL, then how are we going to be able to differentiate what these side effects are from, the chemotherapy and the Decadron, and the one that comes from the heparin?

So I think we have to be careful. You can't

really piggyback everything. Plus I was taught, and I trained at the NCI, that you only do one trial at a time. And so how are you going to do two therapeutic interventions and then dissect?

You were my chair, so you --

DR. REAMAN: I never suggested piggybacking trials. I think the recommendation was maybe using the infrastructure, and I think there's a way to do that. But I couldn't agree more that -- although we have a very long history of asking multiple questions and doing factorial designs, but in this situation, I think you're absolutely right. I wouldn't look at an anticoagulant in combination with a new targeted therapeutic. I mean, they're sort of true-true and unrelated, and there's no reason why they couldn't, shouldn't, be two separate studies.

But you're right. I think -- but as we've been talking, we have been concerned about the incidence of decreased bone mineralization in children with ALL, and we've been resolute in our decision that it's totally related to the use of steroids, and not just all steroids but specifically

Decadron. But who knows how much contribution there could really be from the daily infusion of heparin, even though it's low-dose heparin, for catheters? It's something that no one's ever really looked at or evaluated or studied.

DR. BALIS: Dr. Young?

DR. YOUNG: I'll do the naysayer to the naysayer now. So I don't disagree with what you're saying, Dr. Minniti. But I think, for example, as I'm thinking about this trial design -- and believe me, I've thought about this specific trial design a lot because I obviously submitted a grant for it, so I've been months going over this.

But if we went through, let's say, COG, right -- so there are a number of patients that get ALL. There's a number that are going to go on a certain protocol even; you can just limit it to that. And then within that, as we saw, there's a number that are going to get a clot. And everything else about these patients, otherwise, going forward is more or less the same. It's a fairly uniform population. And then the ones that get a clot get

treated with anticoagulant for three months, six months, however long. And then if you look at bone mineral density across those groups, I think you can -- it is a piggybacking kind of study. But you can try to answer some of those questions at the same time.

Otherwise, you can do it completely separate, which is what I proposed to do, is do it separate and just to answer that one question. So we're hearing some different things; just do one thing. No, let's try to get as many answers as we can from the same study. Let's leverage COG, but don't add another study on.

So we're hearing a little bit of some conflicting things, which is good. I think it brings many different ideas to the table. But I'm just trying to put it all together and say, yes, you can try to get funding for a separate, unique study where you're just looking at issues like bone mineral density -- and, by the way, there is some data on pediatric normal ranges. In my institution, there's a guy who's NIH-funded who just does this for his

whole career, a radiologist. So there is data on normals.

So trying to, again, incorporate all these ideas; let's leverage COG, let's do some combination things, but let's try to answer a unique question, but, again, and back to clinical trial design. So I think there are ways to do all of this.

DR. BALIS: Let's bring in this last question because there are certain parts that overlap here with the C. And I do want to get to it because it's really the framework for which we -- if we're going to make recommendations that would be more specific about clinical trials, it needs to be discussed first.

So the last question is, please identify the specific pediatric thrombotic conditions, patient populations, and anticoagulant products that should have the highest priority for investigation. Please also discuss the clinical conditions for which you would consider prophylactic anticoagulation studies. Elaborate on study design, specific patient populations, age groups, and endpoints.

That's a huge -- what? So we have 10 minutes to discuss it.

[Laughter.]

DR. BALIS: So it's pretty broad --

DR. REAMAN: Can I make a suggestion?

DR. BALIS: Yes.

DR. REAMAN: Let's focus on the first part --

DR. BALIS: Yes.

DR. REAMAN: -- Or maybe the first two sentences. I think the study design will definitely follow. But I think getting some priority of the clinical conditions and situations is really critical to this discussion.

DR. BALIS: Yes, I think it is. And those have come up already, which is why I wanted to just go ahead and get this out, because I think we're talking about a lot of these things already.

The other part of it, from my perspective, it's a new initiative here. We probably shouldn't start too global in terms of trying to do a study with every subspecialty. So it does need to be

focused in.

Dr. Artman?

DR. ARTMAN: Well, I would just, I guess, like to lobby for that Fontan population for several reasons. One is that it is a clinically important problem in that when these patients do develop a thrombosis, it's clearly associated with increased morbidity and mortality in that group. It's clear that they need some anticoagulation therapy or antiplatelet therapy; we know that. And the existing drugs are just not suitable and not effective. So I think that's a clear need.

I think there are sufficient numbers of patients. So in that first Pediatric Heart Network cross-sectional study of Fontan patients, seven centers screened 1,078 patients in a one-year period. These were children aged 6 to 18 years of age. They found 644 were eligible, and enrolled 546, which was an 86 percent consent rate, and that was 10 years ago, in seven centers.

So I think there are sufficient numbers of these Fontan patients out there.

And then thirdly, the existing infrastructure is there in the Pediatric Heart Network. So, to me, that just seems like one that is important and is sort of the low-hanging fruit, would be easy to do.

DR. BALIS: Are you talking about both prevention and treatment studies?

DR. ARTMAN: Well, I think you could do both, certainly. In my estimate, the most compelling would be the prevention trial. But I think that you could easily layer onto that, then, okay? So we didn't prevent. You've had a thrombosis, and then do a treatment arm or arms.

DR. BALIS: Greg, can you address the issue again?

DR. REAMAN: I don't think the Children's Oncology Group will do the trial in the Fontan population.

[Laughter.]

DR. BALIS: Okay. That's not what I was asking, but if you want to verify it --

DR. REAMAN: I just wanted to make that clarification.

DR. BALIS: Yes. I mean, it seems like in oncology, the focus would more than likely be a prevention study since --

DR. REAMAN: I really think it could be both. But I think prevention, particularly given the incidence figures of 30 to 70 percent, would be something to look at. But I think the question of what do you do for the child who has a thrombosis, you remove the catheter and you treat. But how long do you treat and with what do you treat?

So I think both questions would be very pertinent and very important.

DR. BALIS: Yes, Dr. Farrell?

DR. FARRELL: Yes. I have a question. Can you leverage some information if you were to do a prevention trial to then get sufficient information from a treatment trial, knowing that the pediatric patients who need to be treated are probably a much smaller population?

DR. ARTMAN: Yes.

DR. BALIS: Dr. Luban?

DR. LUBAN: So I'd like to lobby for the ICU

and for CPCRN, where at least from my perspective, we see the greater bulk of acute CVC thromboses that have horrific endpoints. Some of those are cardiac, some of those are renal, and some of those are hematologic. They have the one advantage over the neonates and the preemies, who are also a significant concern to me, in that they're usually older and therefore more able to be serially studied.

From the perspective of CPCRN, there is a preexisting group that exists that is very sensitive to acute intervention. And what I don't know about them, unfortunately, is longitudinal follow up. I have no idea whether that is built into many of their studies.

DR. BALIS: Yes, Dr. Young?

DR. YOUNG: So there's a fundamental question that I've been asked many times, for which I don't really know what the answer is. But the question I get asked sometimes is, if there's a clot associated with a catheter, and the catheter, let's say, is removed -- the clot's still there -- and then if there's a clot that develops, say, de novo,

idiopathically, are the clots different? We know the cause is different. But is the clot different?

Then from that falls the question, does the treatment for one and the treatment for the other going to be the same? And then to follow on from that -- and this is where I would be a lumper rather than a splitter, to Naomi's point, which is that if you have a catheter-related thrombosis from a tunneled catheter because you have leukemia, or from a PICC line because you have osteomyelitis and you needed antibiotics for eight weeks, or because you had a dialysis catheter in place because you had acute renal failure from some viral or other bacterial infection, is that all different? And then should we do one study in the renal patients, and one in the cancer patients, and one in the cardiac patients, and one in the osteomyelitis patients, or should we say, these are all catheter-related thromboses, or even include patients that don't have catheter-related thrombosis?

That's where the devil's in the details. As you get more heterogeneous in the population, as we

talked about, that may limit some of the conclusions you can draw. On the other hand, you will accrue a lot more patients. If you're talking about safety, there may be some differences in the patient populations, but maybe you can do some sub-analyses.

So these are some things to think about. With catheter-related thrombosis, are we going to squeeze it down to a certain type of catheter in a certain population, or are we going to say all catheters in all populations, or something in between? And that comes back to the whole clinical trial design issue. But these are things that have to be always thought about.

DR. BALIS: Yes. Dr. Shurin?

DR. SHURIN: Yes. I was just going to point out that Dr. Portman in his presentation gave some data that Dr. Neufeld and Dr. Newburger had put together at Children's. I'm actually sort of amazed to find, since Dr. Newburger is a cardiologist, that this doesn't actually include congenital heart disease. But it gives you some idea which patient groups might be most -- which might be adequate

numbers to study. And they really would include the indwelling catheters, malignancy. There's a small group of inherited, but even in a big referral hospital, it's still a very small subgroup and may not be the one we want to target.

So we sort of really targeted I think what Dr. Young was just talking about, what are the questions that come with it, but really sort of looking at which are the groups, then you figure out who the partners are, and then you really refine exactly what questions you're asking. But really targeting the areas where the people who are managing these patients perceive these as a big problem will make it much easier to do the studies.

DR. BALIS: Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Balis. And I will try to sprinkle in my response some references to some Dennis Quaid movies for Dr. Young.

[Laughter.]

DR. SEKERES: So The Big Easy would be to lump all catheter-related thromboses. But The Right Stuff would involve determining whether these

catheter-related thromboses, in addition to what you've mentioned already, are clinically significant. So you could determine that by what Susan just said, by asking patients whether it's something that needs to be treated, but also whether they actually do eventually lead to thromboembolic events. Right?

I'm not convinced that most upper extremity clots are things that we need to worry about or need to anticoagulate, at least -- and I'm taking to it in an adult perspective. But most of these are not eventually going to lead to a PE. Right? It's not the same as a lower extremity DVT.

The second issue in determining what populations to study really gets to more regulatory issues. So the question that I would pose to FDA is, if you're going to ask that companies going for an approval in a certain drug include pediatric patients, does it have to be for the same indication, or could it be for something that is related?

So, for example, could a company study -- going, for example, for an approval in thromboses related to hip surgery, look at kids who

have catheter-related thromboses?

DR. FARRELL: So a company would be encouraged to submit a proposal to study in a pediatric population. They don't necessarily have to be tied to the adult indication, and so we'd be very happy.

I also want to make a point. We have had sponsors come in to discuss catheter-related thrombolytics, in the renal setting, where they're going to -- I don't know whether their studies are going to be completed or not, but they discussed enrollment of adults and peds in the same trial. And we wanted some adult data first before, of course, we allowed enrollment of pediatric patients.

So there's some sponsors out there thinking about creative ways to get the pediatric data.

DR. BALIS: Yes, Dr. Durmowicz?

DR. DURMOWICZ: Just to add on that, if a sponsor comes in with a new application, PREA, the required assessment in pediatric patients, is indication-specific. So if it comes in for prophylaxis secondary to hip replacement surgery,

that's the indication the sponsor would have to study.

Now, if we can go back and issue a written request under BPCA, then we can ask for whatever we think is needed for that drug moiety.

DR. SEKERES: It's actually an interesting distinction between a company's going to go -- again, I'm speculating; I'm not part of any company. A company's going to go for an indication that's going to yield a lot of market for their product. So they may go for something that's completely an adult indication, like hip replacement, and think, ah-hah, well, we're excluded from looking at pediatrics because they just don't get a lot of hip replacements. But if you were then to tie to this, but wait a second, you need to look at something in pediatrics that's thromboembolic-related, you'd get pediatric data. Right?

DR. DURMOWICZ: Yes. But under PREA, we can't require it under the law. So that's the key thing. Under BPCA, we can request to study Fontan. We can study like dialysis, and that would give them

the incentive, the pediatric exclusivity, to have marketing patent protection for six months.

So the BPCA is more of an incentive program, and the incentive is protecting their patent. So patent half-life, then you still have patent life as well. But PREA is specific to the indication, so we can't make them study another indication.

DR. SEKERES: It's an interesting obstacle to studying pediatric populations.

DR. DURMOWICZ: Absolutely. Absolutely. It's key.

DR. BALIS: Yes, Dr. Suh?

DR. ROBIE SUH: I just wanted to add that for tinzaparin, fondaparinux, and -- I'm blanking on the other one -- and dalteparin, those are the three who have had treatment indications that have come in since passage of the pediatric exclusivity provision. That's why they have existing PREA requirements.

Of course, the difficulty there is that the treatment was in conjunction with oral warfarin, and this has been -- you know, the very short-term treatment with conversion over to the oral warfarin,

and that's been a real clunker in getting studies done.

DR. SEKERES: Well, it seems to me there's some way that you can tie it to related conditions in pediatric populations. Right? So if a drug is going for approval for prophylaxis of thromboembolic events related to atrial fibrillation, then you could tie it to one of the pediatric cardiac studies, possibly.

DR. REAMAN: Not if it's for atrial fibrillation, unless you study it in a pediatric population with atrial fibrillation. That's the --

DR. DURMOWICZ: That's the law.

DR. REAMAN: That's the law. We can ask. We can suggest. We can submit a written request. But a sponsor doesn't have to comply with that request. I mean, they can deny to do any studies. And there's no recourse, and there's nothing -- I mean, the company won't be held responsible for refusing. It's their option and their right to refuse.

DR. BALIS: Yes, Dr. Durmowicz. Go ahead.

DR. DURMOWICZ: Then if the company does refuse, that's when we can work through NIH to see if

it's possible to fund the studies through this kind of off patent or kind of in the situation where the written request is refused.

DR. REAMAN: But then you have to wait a number of years until an agent is off patent. And during that time, hundreds, maybe thousands, of children have received a product with no real safety and efficacy data. And that's why we're here talking about this.

DR. DURMOWICZ: Right.

DR. BALIS: Dr. Young?

DR. YOUNG: Yes. I wanted to ask, actually -- and Dr. Robie Suh's comment is interesting to me because I'm also a bit involved in that.

So if a company develops a drug for initial therapy for prevention of VTE PE, but only in conjunction with conversion to warfarin, then PREA says that that's how it has to be? So in other words, if in pediatrics we rarely convert patients -- I don't want to say rarely, but it's less frequent that we convert patients to warfarin, where

is the drug company held? Are they held to the, well, if we can't get patients -- if we can't get a study done where we convert patients to warfarin, then are we off the hook, or do we do a study where we don't convert to warfarin because we have that indication?

Where do things fall there? Because that is a problem.

DR. BALIS: Yes. Go ahead, Dr. Robie Suh.

DR. ROBIE SUH: Or if that prophylaxis indication was -- as we commonly see in hip and knee replacement surgery, the company argues, reasonably so, that that use, that specific use, that specific indication, that appears in the indication section, is not really markedly relevant to a pediatric population. And under PREA, we cannot require them to study. We can't say, well, it should work for whatever. Now, albeit some of these agents, maybe they may develop it for a treatment indication later.

Now, what has happened again with the treatment indications, particularly for the low-molecular-weight heparins, is that it has been used

as heparin traditionally has been used in conjunction with warfarin, which is, you use that agent initially, the parenteral agent initially, until the warfarin INR is in the therapeutic range, and then discontinue. And it is the continuation of the oral warfarin in pediatric patients that has posed the problem for those agents that fall under PREA because they got their treatment indication after that legislation was passed.

I think the considerations I mentioned in my talk of having long-term safety experience, if you will, a long-term treatment experience with a single parenteral agent for the entire duration of therapy for VTE is something that we really don't have in hand, and certainly was not submitted as part of how the registration trials were done in adults. So there's an additional complication.

Now, again, sponsors can make proposals for how to address the treatment indication, but they'll have to have arguments and support for a modification of the approach, if you will.

You may want to say more.

DR. FARRELL: The agency would always be willing to listen to why a modification was necessary. And I think we've accepted it in other disease areas when there was a serious safety risk associated with giving a particular agent.

DR. YOUNG: Let me just follow up.

So I showed the data from Raffini, where enoxaparin is used four times more than warfarin throughout any pediatric age group, and even more so in the youngest age group.

So this is what I'm asking. So under PREA, some of these low-molecular-weight heparin drugs and fondaparinux, they have a treatment indication; however, only as an initial therapy while you're converting to warfarin.

So under PREA, under the law, do you have to require the company then to do that similar kind of trial, or can you allow modifications, say, look, we know that warfarin is only used in a small percentage of patients, so just give us 20 percent of the patients with warfarin, and then the rest can continue on? Or that's not something that's, because

it's the law, that you can really do? Because, otherwise, you're kind of stuck between a rock and a hard place.

[Laughter.]

DR. ROBIE SUH: Modifications can be allowed, provided they are justified. Particularly with pediatrics, it's having that safety information to support the use, and beyond that, for which we have data available in adults. So it's a negotiating kind of thing, where we have to have the data developed and presented to support.

DR. YOUNG: No. I understand that. Right; so there isn't long-term safety data even in adults, so how can you authorize, per se, to do it in children?

But this is an area where it might be one of those rare instances where pediatric studies can actually inform adult medicine, because in adult medicine, particularly in patients with cancer who have thrombosis, they do tend to end up on these agents for long term because they don't want to use warfarin in those patients. So this is an area where

I think that type of information, which is important for pediatrics, could actually maybe even inform a little bit on the adult side.

DR. BALIS: Yes? Go ahead, Dr. Robie Suh.

DR. ROBIE SUH: I don't know. I guess we might also mention that -- I'm talking specifically now about pediatric studies to address a PREA requirement for these. If a sponsor proposed a pediatric study with some other regimen and duration in pediatric patients, independent, if you will, of PREA, this is not to say that the agency would say, oh, no, that'll go on hold; we'll never let you do that kind of thing. But that's -- I'm sure you understand we're trying to work a lot of things together here in one basket, if you will.

DR. BALIS: Dr. Freedman?

DR. FREEDMAN: I just want to know, with regard to the REMS program, can that be required after regular approval has been given to fill a void, in some instances? In other words, if you feel there's data lacking or information lacking in your label, and there's no movement in satisfying the

studies that need to be done, would you have to wait for a series of events to be reported first in order to activate the REMS?

Is the REMS an option in this situation?

DR. FARRELL: Usually the REMS is written either with a theoretical or known risk. And I would say for some of the drugs to treat or agents to treat thrombocytopenia, we didn't know enough, because we had short-term data, about what the long-term risks were. And for that reason, they went under a REMS.

So a REMS can be helpful. I think the agency has also realized that a REMS sometimes can be a distraction or -- I don't want to say a distraction, but there can be some problems in carrying out a REMS. And so I think we try to look very judiciously at when we want a REMS and when we don't want a REMS.

They're only instituted at the time of initial approval. That's correct.

A sponsor is welcome, by the way, to come to see us to discuss a pediatric indication even if a drug does not have an adult indication, to talk about development there.

DR. BALIS: One of the parts of this last question relates to identifying the products that we think would have the highest priority. I'm not sure that this group, the way it's constituted, is the best one to make that decision.

But do you want to comment on that, Dr. Young, in terms of what you think would be best?

DR. YOUNG: So I go around the country periodically, giving a talk on anticoagulants. I just did one last week where I did my residency for Grand Rounds. And I start off that talk by saying that we have unfractionated heparin, we have low-molecular-weight heparins, and we have warfarin, so why do we even need to study any of these other drugs? And then I go through the list of reasons why these particular drugs are problematic, and obviously we've discussed a lot of that today, and everybody's aware of thought.

So I think that there is definitely a need for better anticoagulants, as there is in adults, in children as well, better in terms of safety, in terms of efficacy, in terms of other side effects, in terms

of ease of administration, et cetera.

So I'm really encouraged that there are a lot of these programs going on with different, new oral anticoagulants. And I think that the day that I don't have to have an INR on my table that I need to review with my nurse to decide what to do is the day I'm looking forward to. And I realize that that's many years away, probably, but I think that would be an advance for all medicine, but definitely an advance for pediatric medicine.

I think what shouldn't get -- what I hear a lot when I go to meetings where they talk about adult thrombosis is that these drugs, give it some time. They're just going to take over. We're not going to see low-molecular-weight heparin any more, or fondaparinux, or these other drugs, because these are just so much better, easier, safer, et cetera.

I think that the one thing we do need to remember in pediatrics is -- I mentioned this point before -- is I think that despite all this push for oral, oral, oral, which I think is a good thing, there's still going to be a need for chronic

parenteral drugs. I'm not talking about unfractionated heparin or bivalirudin in the hospital but for outpatient chronic parenteral drugs because, as we discussed before, sometimes it's very difficult to administer oral drugs to children. And then there are children with chronic illnesses in which they don't absorb oral drugs, the gastrointestinal disorders, which we didn't even bring up, and the chronic TPN, which is another area where we see a lot of thrombosis.

So I think, no, I wouldn't -- I mean, the short answer is I don't think I would prioritize any of these agents. I would just say, to the agency in particular, is that just because all these new things are coming, that there's still going to be some place for some older ones, maybe not heparin or warfarin, unfractionated heparin or warfarin, but for some of these other low-molecular-weight heparins and fondaparinux, that there'll be a role for those probably in pediatrics for many years to come.

I doubt new companies are going to be developing parenteral anticoagulants; I'm not aware,

since the push is so much for oral. But I think that the agency needs to be aware that those other drugs are going to be used in kids, and we need to do the best we can. I keep coming back to the logo, protecting and promoting their health.

DR. BALIS: Thank you.

Any other questions or comments?

[No response.]

DR. BALIS: Did we address all the issues the FDA wants to hear from us on, and do you have any other comments to make at the end?

DR. REAMAN: I think you've addressed all of the issues that we had hoped would come up in the discussion. And as was stated at the beginning, there was not going to be any votes, and we certainly haven't come to any conclusions, moving from movie stars to naysayers. But I think we've received a lot of very useful and important information. And I think if we've inspired some interest in the investigator community and with industry to move forward with some of these suggestions or recommendations, then I think we've accomplished what

we had hoped we would accomplish here.

DR. BALIS: Good. Thank you.

DR. REAMAN: Thank you all.

Adjournment

DR. BALIS: Yes. I thank everybody for coming. There was a lot of good insight, from my perspective. This isn't something I'm an expert at. I think I've learned a lot today. And I do hope that bringing these subspecialties will help in promoting these studies going forward.

Thank you all.

(Whereupon, at 3:20 p.m., the meeting was adjourned.)